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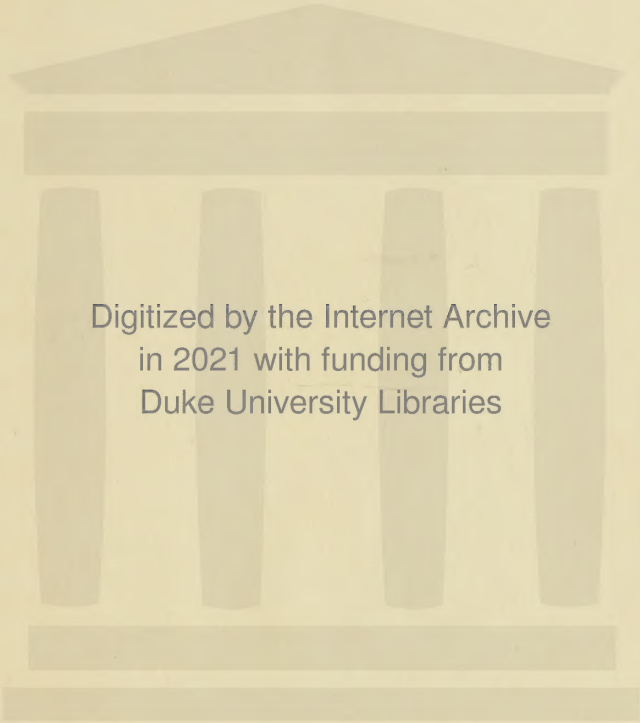

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DUKE UNIVERSITY PUBLICATIONS

MEDICAL GENETICS

By the Same Author

BLOOD GROUPING IN CLINICAL AND LEGAL MEDICINE

and

THE PRINCIPLES OF HEREDITY

MEDICAL GENETICS

A Series of Lectures
Presented to the Medical Schools of
Duke University, Wake Forest
College, and the
University of
North Carolina

By Laurence H. Snyder, Sc.D.
Professor of Medical Genetics
The Ohio State University

Durham, North Carolina
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Foreword

The belief that nothing practical is known about human heredity, except that red hair and hemophilia run in families, has been too prevalent among the public and unfortunately also among many members of the medical profession. To fill this void in the medical students' and physicians' knowledge of medical genetics, and to prevent some of the earlier mistakes in genetic advice to families, the Carnegie Corporation made it possible for Dr. Laurence H. Snyder, Professor of Medical Genetics of the Ohio State University College of Medicine, to spend three months in North Carolina lecturing at the medical schools of Duke University, Wake Forest College, and the University of North Carolina. He also collaborated with Dr. William Allan, of Charlotte, North Carolina, who for many years has been doing pioneer work in human heredity and family records.

Those of us who have heard Dr. Snyder's lectures, now realize not only that much is known of medical genetics but that the knowledge is of practical value in the diagnosis and prognosis of disease, and in the everyday practice of medicine. For example, in addition to the valuable advice which can be given to prospective parents with a poor heredity on the inadvisability of having children, mothers who have had one abnormal child should be cautioned that subsequent ones also may

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be malformed. Physicians who are genetically interested in the family histories of their patients can be on the alert for the development of certain diseases and during the early, usually overlooked stages, can start treatment which may prevent disastrous consequences.

The interest in human heredity which Dr. Snyder has aroused in the Staff and students at Duke University School of Medicine has caused us to persuade him to have these lectures published. Not only do we need a written record of them for frequent reference, but we feel that others should have the advantage of this information. This book will also stimulate interest in and further investigation of the subject. We wish to record our gratitude to him and to the Carnegie Corporation for making these lectures possible.

WILBURT C. DAVISON.

Preface

This book is based on a course of lectures which were given to the sophomore class at the College of Medicine of the Ohio State University for the past eight years, and which were in 1941 expanded and somewhat rearranged and presented to the entire student body of the medical schools of Duke University, Wake Forest College, and the University of North Carolina under the auspices of the Carnegie Corporation. Chapter 1 follows the general outline of an article which I published in the *Ohio State Medical Journal,* December, 1933; and part of chapter 3 was originally presented at an invitational symposium of the Medical Section of the American Association for the Advancement of Science at Richmond in December, 1938, and subsequently published as part of the symposium under the title *Mental Health.* I am indebted to both these sources for permission to rewrite and publish these two chapters here.

It is obviously impossible to give an adequate account of the basic principles of genetics in a short series of lectures on medical genetics. These lectures have dealt strictly with medical conditions and their practical applications. Nevertheless, an attempt has been made to outline the more important kinds of hereditary behavior in such a way as to make them understandable. This has been done in connection with specific traits the first time that

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each major kind of hereditary behavior is encountered. Chapter 4, in which the various genetic mechanisms are first met with in the connection with eye abnormalities, will, it is hoped, provide a working acquaintance with the main kinds of genic action.

Following some general principles in chapter 1, and the medicolegal applications of hereditary traits in chapter 2, the various medical conditions are discussed system by system. Wherever possible, the name of a medical condition has been followed in parentheses by the name of the original describer and the date of the description. Frequent references have been made in the text to the work of individual authors who have described the genetic backgrounds of various traits. No attempt has been made to provide a complete bibliography. At the end of the book a few major references have been listed, from the bibliographies of which may be derived many individual citations. The various medical indices may be consulted for specific references by using the names and dates given in the text.

Figures 6, 9, 10, 11, 12, 15, and 21 are taken from the files of the Duke Hospital; figures 13, 16, and 17 from the files of the Family Record Office of Charlotte, North Carolina; and the family histories from my own files.

I wish to express my deep appreciation to the Carnegie Corporation for making these lectures possible, and to the staffs and student bodies of the three North Carolina medical schools for making my visit both pleasant and profitable.

L. H. S.

Durham, North Carolina
March, 1941

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MEDICAL GENETICS

1

The Study of Human Heredity

In recent years a considerable body of knowledge on the subject of human heredity has been accumulated. Progress is being made rapidly at present and will be made even more rapidly in the near future. It is therefore of advantage to the medical student to become familiar with the present knowledge of human heredity, incomplete though it may be, in order to be able to evaluate the statements and articles of the future as they may appear.

Even in our present state of limited knowledge, an understanding of the hereditary factor in various human conditions can be of very practical value to the physician. Specific examples will be brought out as the lectures progress. Such a knowledge may be applied in several ways.

1. It may be of aid in diagnosis, especially early diagnosis.
2. It may be of service in outlining preventive measures.
3. It may be applied in medicolegal cases.
4. It may furnish the basis for advice on prospective marriages.
5. It may furnish the basis for advice on prospective pregnancies.
6. It may provide the necessary information for set-

ting up eugenic and euthenic programs for the protection of society, in which every physician should be able to take an intelligent part, based upon experimental data, not opinion, prejudice, and overexaggerating the uncertainties.

The study of human heredity has of course grown out of the experimental analysis of other organisms. It is assumed, on adequate grounds, that most of the great fundamental principles of heredity are now known. The work of the past forty years on a large variety of animals and plants has resulted in the establishment and understanding of these principles. It is now imperative to apply these principles to the various morphological, physiological, and pathological conditions in human beings, to test their validity in such conditions.

The carefully controlled experiments in laboratory animals and plants have carried heredity far beyond the old and well-known simple laws of Mendel. These laws stand today just as sound and basic as ever, but many additions and modifications have been made. Improvements in methods of investigation have resulted in bringing a wide range of seemingly inexplicable phenomena under a unified set of hereditary laws, which, while considerably more extensive and inclusive than Mendel's original laws, are yet fundamentally simple and orderly.

No longer does the familiar 3:1 ratio cover the major portion of the field of heredity. As a matter of fact, ratios of the sort found in the F_2 generations of animals and plants are not observable as such in man. No single human family is large enough, as a rule, to provide a valid ratio in any generation. And when groups of families are lumped together for analysis, aberrant ratios

are obtained because it is usually impossible to separate homozygous parents from heterozygous parents. This leads to a radically different type of analysis of human pedigrees, the study of the frequencies of the factors concerned.

Even though we could isolate definite Mendelian ratios in man, the simple 3:1 ratio and others equally obvious would not suffice to explain the whole of human heredity. At least a dozen major kinds of hereditary transmission are known, and the combinations and interactions of these with each other and with the environment increase the number. The three main kinds of genic behavior are dominant, recessive, and blending; and factors (genes) showing such behavior may be autosomal, sex-linked, sex-influenced, sex-limited, lethal, epistatic, multiple alleles, or multiple factors. Definitions and examples of these various kinds of hereditary factors and their behavior will be worked out from time to time in the following chapters.

These various kinds of hereditary behavior have been scientifically established in animals and plants. Human beings, in so far as they have been studied, appear to obey the same laws of heredity as other organisms. The only essential difference is that human beings are capable to a large extent of controlling their own environment. Environment may profoundly modify the *expression* of a hereditary factor, but it neither obviates the *fact* of the genetic nature of any hereditary condition, nor changes in the least the potentiality or the mode of its transmission.

The various kinds of hereditary behavior now known are complicated enough, then, that their understanding

requires a certain amount of study. This means that no one is justified in stating on his own responsibility that a given trait is or is not conditioned by hereditary factors *unless* (1) he is thoroughly familiar with the known kinds of hereditary behavior; (2) he is familiar with the condition under discussion in all its varying manifestations; and (3) he has carefully investigated and analyzed the condition in a scientific manner from a genetic standpoint.

As in other sciences, any hypothesis of heredity, besides accounting for a certain body of facts, must stand the acid test of *predictive value*.

In order to apply a knowledge of heredity to medical practice, certain fundamental conclusions must be granted, and certain common misconceptions correctly understood. Among the conclusions taken for granted in this series of lectures are the following.

1. The biological basis for the dozen or more kinds of hereditary behavior to be discussed has been adequately established by experimentation.

2. Numerous hereditary factors are associated with the chromosomes.

3. Man fulfills the biologic requirements for being subject to the same laws of heredity as other organisms. (Among these requirements are sexual reproduction, a chromosome mechanism undergoing meiosis, physiologic processes similar to those of other organisms, etc.)

4. Mental traits have their basis in physicochemical structure, and thus may be susceptible to the same laws of heredity as other characters.

5. Heredity and environment are cooperative in the production of any finished character. One or the other

influence may in certain circumstances appear negligible, but the dual nature may always be demonstrated. This point deserves a little amplification. We may arrange characters roughly in a series, depending on the relative importance of heredity and environment in their development. At one end would be those in which environment is the major influence, heredity being so similar in all the individuals involved as to play no part in observed variations. Such a character would be syphilis, for example, in regard to which everyone, so far as we know, is constitutionally susceptible, so that whether or not a person contracts syphilis depends entirely on the environmental contact with the causative agent. At the other extreme would be characters in which heredity is the major influence, no environment of sufficient potency to alter the expression of heredity being readily available at present. Such a character would be migraine, for instance, where a person develops the condition regardless of environmental influences if he inherits the factor for it, and where migraine does not develop if the factor is not inherited; the inheritance in this case being directly from one or the other parent.

Between these two extremes lie the great majority of characters, in the production of which heredity and environment play more or less equal roles. The determination of the exact part played by heredity or by environment in the production of any character is one of the most difficult problems in the study of human heredity. Here the use of identical twins has become of paramount importance. We have become accustomed to speaking of a character as "hereditary" when variations in the development of the character are caused mainly

by differences in the genetic make-up. While this is perhaps the accepted use of the word, it must be realized that "hereditary" is a relative term, all characters being, as stated, components of hereditary and environmental influences.

There is no fundamental distinction between (a) the case of a person who inherits a normal structure of the cochlea, the eighth nerve, etc., and so has the ability to hear, and who through disease becomes deaf, and thus pathological, and (b) the case of a person who inherits hemophilia, a pathological condition, and who through recurrent preventive transfusions at regular intervals fails to exhibit the bleeding, and thus becomes essentially normal. In the case of acquired deafness, the original hereditary normal structures will be transmitted in spite of the adventitious deafness; and in the case of the hemophiliac who because of preventive transfusions never bleeds abnormally, the original hereditary hemophilic condition will be transmitted in spite of its lack of manifestation.

Among the misconceptions which are commonly met with, and which must be recognized as misconceptions, are the following:

1. That students of heredity believe and are anxious to prove that all characters are rigidly determined by heredity.

2. That if a character were conditioned by heredity it could not be modified by the environment.

3. That if a hereditary basis were demonstrated for any particular condition, medical research on that condition could not or would not make further progress.

4. That because a causative agent is known for a disease, heredity can play no part in its manifestation.

5. That heredity or "constitutional basis" is a catch-all for the things about which nothing is really known.

6. That a condition cannot be hereditary unless it presents a clear "family history."

7. That "congenital" and "hereditary" mean the same thing.

8. That because in many cases we do not know just how a hereditary factor or set of factors brings about the production of the finished characters, the mere fact of heredity is meaningless.

None of the eight statements listed above is true.

It would be misleading to conclude these general statements without pointing out that in the bringing together of medicine and human heredity, the science of heredity may expect to receive great benefit from the association. Much of human heredity is still to be investigated, and much of the future investigation must be done by those trained in medicine. The question of the exact meaning of susceptibility and immunity in various conditions; the embryologic and developmental means whereby a hereditary factor produces its finished character; the entree to families in which medical traits are found; the understanding of the various manifestations which a given trait may take—all these are questions in which genetics is dependent upon medical advice. It is hoped that this series of lectures may be mutually beneficial.

2

Medicolegal Applications

There are several criteria which must be met by any trait if it is to be used in medicolegal cases from a genetic standpoint. These criteria, first clearly set forth by Wiener, are as follows:

1. It must be so objective and so sharply defined as to give comparable results to all qualified observers.
2. It must be constant throughout life.
3. It must be inherited according to an exact known mechanism.
4. It must be common enough in the population to be of practical use.

Thus far only two traits have completely met these qualifications. They are the blood groups (the AB reaction) and the blood types (the MN reaction).

The blood groups were discovered by Karl Landsteiner, who about 1900 observed that when the serum of one person was mixed with the red cells of another person, one of two things happened. In some instances the red cells of the one were caused to agglutinate by the serum of the other; in other cases no agglutination occurred. Heteroagglutination had previously been known, but this was the first recorded case of isoagglutination. Landsteiner, recognizing this as an antigen-antibody reaction, realized that there must be present in the red cells of

certain persons a specific antigen, and in the serum of others, a specific antibody.

Further work by Landsteiner and his co-workers revealed the fact that there were two such antigens which might be present in human red blood cells, each having its specific antibody. These antigens were named for convenience A and B. Tests showed that any individual might have in his red cells antigen A, or antigen B, or neither, or both. Moreover, there is a reciprocal relationship between the presence of each of these antigens and the presence of its specific antibody, so that any individual either has antigen A or else the antibody against A, and either antigen B or else the antibody against B.

There are thus four sorts of people in the world on the basis of these two antigens: those having antigen A in their cells (spoken of as belonging to group A), those having antigen B (group B), those having both antigens (group AB), and those having neither antigen (group O). The reactions of the serum and cells of each group are shown in table 1.

TABLE 1.—*The Effect of the Serum and the Response of the Red Cells in Each of the Four Blood Groups*

Group	*Effect of serum*	*Capacity of cells*
O	Agglutinates cells of A, B, AB	Not agglutinated by any serum
A	Agglutinates cells of B and AB	Agglutinated by serum of O and B
B	Agglutinates cells of A and AB	Agglutinated by serum of O and A
AB	Does not agglutinate any cells	Agglutinated by serum of O, A, B

The letter system of naming the groups is rapidly supplanting the older roman numeral systems. This is made expedient because of the fact that two investigators, Moss in America and Jansky in Europe, independently and differently numbered the groups. The resulting confusion led to the adoption of the letter system. Table 2 shows the correlations of the three systems.

TABLE 2.—*Comparison of the Old and New Systems of Naming the Blood Groups*

Jansky	*Moss*	*Letter*
I	IV	O
II	II	A
III	III	B
IV	I	AB

To determine the blood group to which a person belongs, we simply determine whether his cells contain either, both, or neither of the antigens. Now we can determine that an antigen is present only by its reaction with its specific antibody: in this case by noting whether or not agglutination occurs when the unknown cells are mixed with a known antibody, the cells being in suspension when the antibody is added. Although the antigen, if it is present at all, occurs in all the cells of the body, red blood cells are generally used to demonstrate its presence since such cells may be readily placed in suspension in normal saline solution. Likewise antibodies, which when present occur in a variety of body fluids, are normally derived from serum because of its ready availability. The antibody against A is of course obtained in serum from persons of group B, and the antibody against B in serum from persons of group A.

Geneticists early became interested in the possible inheritance of the four blood groups. It was first important to determine how early in life the blood groups are established, and whether or not they remain stable throughout life. In many laboratories it has been proved that the antigens are established at birth or very shortly thereafter, and that they remain fixed and stable throughout life, even under such extreme environmental factors as illness, etherization, irradiation, dietary factors, and the administration of various drugs.

The blood groups, then, occurring as fixed biochemical entities, offer a unique opportunity for genetic studies. Such studies were originally undertaken with no thought of practical applications, but important applications have nevertheless developed from them.

Thousands of family histories gathered during the last twenty years in all parts of the world have given consistent results. The various possible matings and the children who may result from them are listed in table 3.

TABLE 3.—*The Inheritance of the Blood Groups*

Mating	*Offspring*
O and O	O
O and A	O, A
A and A	O, A
O and B	O, B
B and B	O, B
A and B	O, A, B, AB
O and AB	A, B
A and AB	A, B, AB
B and AB	A, B, AB
AB and AB	A, B, AB

The inheritance illustrated by this table is a type well known to the geneticist. The results indicate that the blood groups are inherited as a set of three alleles (Bernstein, Snyder, Wiener, et al.). Alleles are hereditary factors, or genes, occupying a particular locus on a chromosome, so that only one of the alleles may occupy that locus at one time.

Several simple laws are evident from the type of hereditary behavior seen here. First, antigen A never appears in the blood of a child unless it was present in the blood of at least one of the parents. Second, antigen B never appears in the blood of a child unless it was present in the blood of at least one of the parents. Third

(because there are three alleles involved), a parent of group O can never have a child of group AB. Fourth, for the same reason, a parent of group AB can never have a child of group O.

The three alleles are as follows: a gene A, accounting for the presence of antigen A; a gene B, which accounts for the presence of antigen B; and a gene O, which does not produce either antigen. Genes A and B are dominant to gene O, but not to each other. Table 4 shows the genetic constitution of each of the four groups.

TABLE 4.—*The Genetic Constitutions of the Blood Groups*

Group	*Genetic constitution*
O	OO
A	AA or AO
B	BB or BO
AB	AB

The first practical application of these results is found in those relatively rare cases where infants may have become inadvertently mixed in a hospital. For example, in a recent case two mothers went home from the hospital, each with a new baby. Upon bathing her baby, Mrs. B found a label on the baby's body with the name "W." Upon consulting the W family, it was found that the baby in that home was labeled "B."

To straighten the matter out, a court case was invoked, as a result of which blood tests were made. The W parents were both of group O, and the baby they had taken home with them was group A. The B parents were of groups O and AB, respectively, and the baby they had taken home was group O. Reference to table 3 will show that neither set of parents could have produced the child which they took home from the hospital. On the other

hand, each set of parents could have produced the other child. The court, on the basis of this evidence, ordered the babies exchanged, and the perplexing problem was settled on the basis of the known heredity of the blood groups. Not all cases could be settled on this basis, since both infants might be of the same group, or it might be that either set of parents could have produced either child.

Fortunately, cases of the sort just described are rarely encountered, but another type of practical application is unfortunately all too often met with. This application involves cases of disputed paternity. Such cases take several forms. For example, a girl gives birth to an illegitimate child and accuses a certain man of being the father. He denies the paternity, and a court case results. Again, a husband accuses his wife of an affair with another man, and claims that the last child of his wife is not his own. Divorce proceedings lead to an investigation of the paternity.

In such cases we may take the results shown in table 3 and turn them around; in other words, if we know the blood groups of a child and of one parent, we can predict what the blood group of the other parent must be. For example, if a child is of group A and the mother is of group O, then we know that the antigen A in the child's blood must have been inherited from the father, who therefore must have antigen A in his blood. To state this conclusion in another way, the father could not belong to group O or to group B. It is thus sometimes possible to clear a man who may be wrongly accused of being the father of a certain child. The conditions under which this may be done are listed in table 5.

TABLE 5. *The Medicolegal Applications of the Blood Groups*

Group of child	*Group of one parent*	*Other parent could not be in group*
O	O	AB
O	A	AB
O	B	AB
A	O	O or B
A	B	O or B
B	O	O or A
B	A	O or A
AB	A	O or A
AB	B	O or B
AB	AB	O

In 1928 it occurred to Landsteiner that antigens might be present in human cells for which no normal antibodies existed in the serum. If such antigens did exist, they could be demonstrated by injecting human red cells into experimental animals, and then testing the serum of such animals against cells of the donor. Experiments of this nature, using rabbits, revealed the presence of two agglutinable properties in human cells, unrelated to antigens A and B and unrelated to the normal heteroagglutinogens. The new antigens were named M and N (Landsteiner and Levine 1928). It is found that every person has in his cells either antigen M, or antigen N, or both, resulting in three blood types.

Exhaustive tests in many laboratories of the establishment, stability, and heredity of the new antigens have demonstrated that, as with the A and B antigens, the M and N substances are established at the time of birth, are subsequently stable, and are inherited in a clear and recognizable manner. Their inheritance as a single pair of alleles without dominance is shown in table 6, and their medicolegal application in table 7.

TABLE 6.—*The Inheritance of the Blood Types*

Mating	*Offspring*
M and M	M
M and N	MN
N and N	N
M and MN	M, MN
N and MN	N, MN
MN and MN	M, N, MN

TABLE 7.—*The Medicolegal Applications of the Blood Types*

Type of child	*Type of one parent*	*Other parent could not be in type*
M	M	N
M	MN	N
N	N	M
N	MN	M
MN	M	M
MN	N	N

Both sets of tests are made in disputed paternity cases. Sometimes an exclusion is made on the basis of the AB reaction, sometimes on the basis of the MN reaction. In either case it is valid and supported by thousands of family histories.

European courts were quick to recognize the value of the tests in disputed paternity cases; and many such cases were recorded, even before the discovery of the MN reaction, from Denmark, Norway, Sweden, Germany, Austria, Danzig, Lithuania, Czechoslovakia, Holland, Japan, Russia, Belgium, and Ireland. The Latin countries still hold to the dictum "Pater semper incertus," and their courts have not freely allowed the possibility of a biological test of fatherhood.

American courts have been slow to accept the admissibility of the tests. The first recorded case in this country occurred on January 2, 1934, before Supreme Court Justice Steinbrink of the State of New York. Since then

other cases have occurred, and there are now laws governing the use of the tests in New York, New Jersey, Ohio, and Wisconsin. The Ohio Laws are printed as an appendix to this chapter.

It is clear that when we are called upon to make blood tests for paternity, our answer may be one of two statements. We may say, "This man could *not* be the father of the child in question." Or we may say, "This man *might be* the father of the child." We can never say, "This man *is* the father of the child." If the results of the test clear the man, they may be admitted as legal evidence. If they do not clear the man, they are of no use whatsoever as evidence.

The chance that a man who is falsely accused will be cleared by the blood tests is about one in three. In the other cases he will by chance be of the required blood group and type even though not the actual father. In practice the proportion of exclusions will be less than one in three, since many men who are justly accused will take the tests because they have nothing to lose thereby. In New York, out of the first 150 cases under the new law there were 15 exclusions (Wiener). In Ohio out of fifty cases we have had seven exclusions.

In 4,818 cases recorded from all countries in recent years since the use of the MN tests, there have been 834 exclusions, or 17.3 per cent. Since if all accused men were innocent there would have been about 33 per cent exclusions, it follows that only one half of the accused men were actually the true fathers. Considerable injustice must therefore be done by the procedure of permitting the woman in such cases to name the father of her child. Blood tests can help to correct this injustice, and

the fear of being charged with perjury will tend to lessen false accusations.

Careful studies in our laboratory have convinced us that the blood group and blood type of an infant can be determined accurately at birth by testing the agglutinogens, even though the agglutinins may not be fully developed. To be absolutely on the safe side, the tests, however, should be made after the infant is a month or two old.

Recently various new antigens have been added to the older substances. The most useful of these up to the present moment are the subgroups of group A.

If serum of group B (which contains the antibody against antigen A) is mixed with ¼ its volume of packed washed cells of group A, and exhausted for an hour at room temperature, the antibody against A should be removed. However, only certain A cells remove all the antibody. Cells from other persons of group A leave an antibody which will agglutinate certain A cells.

There would thus appear to be two kinds of A cells and two kinds of antibodies corresponding to these antigens. The two antigens are known as A_1 and A_2. Cells of A_1 will remove both antibodies from B (or O) serum. Cells of A_2 will remove the antibody against A_2, but will leave an antibody against A_1.

Serum of group B absorbed with cells of A_2 may then be used to differentiate A_1 and A_2 cells. If the unknown cells react with the absorbed serum, they are A_1 (or A_1B). If they do not react, they are A_2 (or A_2B).

There is still some discussion as to whether the two types of antigen A are truly qualitatively different or only quantitatively different. The evidence appears to

be sufficient that they are actually qualitatively different, that is, that there exist two antigens and two corresponding antibodies within the old group A. Table 8 presents the medicolegal applications of the subgroups of group A.

TABLE 8.—*Medicolegal Applications of the Subgroups of Group A. To Be Used If the Orthodox Blood Tests Do Not Clear the Accused, and If, in Addition, the Child Is of Group A or Group AB.*

Group of child	*Group of one parent*	*Other parent could not be in group*
A_1	A_2	O, A_2, B, A_2B
A_1	A_2B	O, A_2, B, A_2B
A_1B	B	A_2, A_2B
A_1B	A_2B	A_2, B, A_2B
A_2	O	A_1B
A_2	A_1	A_1B
A_2	A_2	A_1B
A_2	B	A_1B
A_2B	B	A_1B
A_2B	A_1B	B, A_1B

Other interesting applications of the blood groups occur in transfusions, pathology, and anthropology. For a full discussion of these points consult Snyder 1929, Boyd 1939, and Wiener 1940.

The Ohio Laws on Blood Grouping

§12,122-1. *Paternity tests in illegitimacy proceedings.*

Whenever it shall be relevant to the defense in a bastardy proceeding, the trial court on motion of the defendant, shall order that the complainant, her child, and the defendant submit to one or more blood-grouping tests to determine whether or not the defendant can be excluded as being the father of the child. The tests shall be made by duly qualified physicians or other qualified persons, not to exceed three, to be selected by the court, and under such restrictions and directions as the court or judge shall deem proper. In cases where exclusion is established the results of the tests together with the finding of the expert or experts of the fact of non-paternity shall be

receivable in evidence. Such experts shall be subject to cross-examination by both parties after the court has caused them to disclose their findings to the court or to the court and jury. Whenever the court orders such blood-grouping tests to be taken and one of the parties shall refuse to submit to such test, such fact shall be disclosed upon the trial unless good cause is shown to the contrary. In the event such tests have been made prior to the trial, the results thereof shall be receivable in evidence. The court shall determine how and by whom the costs of such examination shall be paid. (118 v. H. 213, 1. Eff. Sept. 2, 1939.)

§12,122-2. *Paternity tests in civil or criminal actions.*

Whenever it shall be relevant in a civil or criminal action or proceeding to determine the paternity or identity of any person, the trial court on motion, shall order any party to the action and any person involved in the controversy or proceeding to submit to one or more blood-grouping tests, to be made by duly qualified physicians or other qualified persons not to exceed three, to be selected by the court and under such restrictions or directions as the court or judge shall deem proper. In cases where exclusion is established the results of the tests together with the findings of the expert or experts of the fact of non-paternity shall be receivable in evidence. Such experts shall be subject to cross-examination by both parties after the court has caused them to disclose their findings to the court or to the court and jury. Whenever the court orders such blood-grouping tests to be taken and one of the parties shall refuse to submit to such test, such fact shall be disclosed upon the trial unless good cause is shown to the contrary. The court shall determine how and by whom the costs of such examination shall be paid. (118 v. H. 213, 1. Eff. Sept. 2, 1939.)

3

Mental Disorders

Having discussed factors which are simple in nature and relatively easy of analysis, let us turn our attention to the other end of the scale, and take up mental traits, which are very difficult to analyze genetically.

Geneticists have, in general, two methods of attacking problems of human inheritance. In the case of characters which are known to be influenced but little by ordinary variations in the environment, the collection of family histories and their careful analysis by the newer statistical technics provide the simplest and surest means. Recent statistical analyses involving the paired sib method, the gene frequency technics, and the estimation of linkage probabilities, have been brought to a high degree of perfection by workers both in this country and abroad (e.g., blood groups).

The second method, necessary in those cases in which a certain proportion of the observed variance is to be ascribed to environmental influences, or in which the effects of such environmental influences are to be tested, necessitates a different technic. In the case of many of the so-called mental traits, where the variance ascribable to environment is admittedly large, the mere study of family histories as such will give no clue to the true basis of these traits. Here we must use methods designed to discriminate between the causes of the variance.

Geneticists no longer ask, "Is this trait due to heredity or to environment?" Instead, the question now reads, "How much of the variance in this trait, if any, can be due to differences in the genetic make-up of the individuals concerned, and how much, if any, can be due to differences in the environments to which they may be exposed?" For any specific population we may ask the specific question, "How much of the variance in this trait is due to genetic variability and how much to the exigencies of the environment in which the population has developed?"

To answer the general question it is necessary to accomplish two things: first, to keep the heredity constant while the environment is made to vary, and, second, to keep the environment constant for a series of genetically variable individuals. Once the general question is answered for any trait, the causes of the variance for that trait in a specific group may be estimated from a study of the genetics and the environment of that group.

The two necessary points outlined above are not easy of accomplishment in the study of human beings. Fortunately nature and society have come to our aid; nature by providing twins, identical and fraternal, and society by providing orphan asylums, foster homes, and the like for the rearing of children who for some reason have been deprived of their parents.

In order that there may be no misunderstanding, let us clearly define what we mean by heredity and by environment. I have already said that for purposes of our discussion the term *heredity* is taken to connote the mechanism of the chromosome and the gene, operating under the biologic laws of segregation, random assort-

ment, linkage, crossing-over, and similar phenomena. In this category would also be placed cytoplasmic inheritance, should the possibility that this type of transmission can occur ever become an established fact.

Environment, on the other hand, is taken to include such things as formal schooling, language handicaps or advantages, diet, cultural status of the home and of the community, sanitary conditions of the home and of the community, subjection to propaganda, persecution or oppression, exposure to accident or to the etiologic factors of disease, prenatal influences, and other agents of a like sort. Here, as in heredity, *variation* in respect to the agents involved and the resulting variance observed for the trait constitute the points at issue.

In the analysis of mental traits, not only are we faced with difficulties of ascribing to hereditary and environmental differences their proportionate shares of the variance, but two further impediments stand in our way. These are, first, the paucity of objective measures of the traits we seek to study and, second, the almost complete lack of objective tests of environment. Much work remains to be done along these lines. When we have overcome the difficulties of classification and diagnosis of mental traits, and of evaluation and description of environments, we shall have gone a long way towards solving the problems of the constitutional and genetic bases of mental disorders.

But I would not appear to be pessimistic. In spite of difficulties and handicaps, much careful research testifies to the fact that in addition to recognized environmental factors there are genetic variations which play their part in producing variance in the nervous dis-

orders, the psychoses and the mental aberrations. There are certain neurological diseases in which genetics plays a prominent part and in which environmental influences take only a minor role; for example, Huntington's chorea, amaurotic juvenile idiocy, and paralysis agitans (shaking palsy). I will return to these. Let us turn our attention now chiefly to dementia praecox and the manic-depressive psychosis, in which the role of the environment may be relatively large. Here the study of twins has become of primary importance.

Galton in 1883 first called attention to the fact that the biology of monozygotic twins as contrasted with that of dizygotic twins affords a means of distinguishing between the effects of tendencies received at birth and those that were imposed by the special circumstances of their afterlives. In spite of this clear statement many later reports on mental disease in twins have failed to distinguish between the two types. Recent researches by Lange, Luxenburger, Legras, Humm, and, finally, by Rosanoff and his co-workers offer critical evaluation of the nature-nurture problem on the basis of a clear diagnosis of monozygosity and dizygosity. Occasional isolated cases, such as those reported by Merriman, Franz, and Parker, also are of importance. These various findings have been recently collected and critically summarized by the Committee of the American Neurological Association for the Investigation of Eugenical Sterilization.

Dementia praecox (Morel 1857, Kraepelin 1898). A study of the findings indicates that in cases where one member of a pair of twins has dementia praecox, the other member, if they are monozygotic, also has it in a large proportion of the cases (68 per cent in Rosanoff's

cases, a somewhat higher proportion in those of other investigators). If, however, the twins are dizygotic, the second member of the pair develops dementia praecox in a relatively small proportion of the cases (15 per cent in Rosanoff's findings, a somewhat smaller proportion in the findings of other investigators). Rosanoff's work is of especial value since the material is unselected, whereas most other reports have been on selected cases.

It is to be noted that there is a marked contrast between monozygotic twins and dizygotic twins with respect to the proportion of cases of both twins of the pair affected. Monozygotic pairs are not always identical in the affection of the two members, however, so that genetic influences, while they must be recognized, cannot account for all the observed variation.

Rosanoff, Handy, Plesset, and Brush draw the following conclusions from the results of the studies of twins, which conclusions, it may be stated, are concurred in by the above-mentioned Committee:

1. In the etiology of so-called schizophrenic psychoses hereditary factors seem to play an important part.

2. The hereditary factors, in themselves, are often inadequate; that is to say, they do not suffice to produce a schizophrenic psychosis.

3. The pathogenic effect of the hereditary factors is not highly specific. Other factors often play a part with resulting dissimilarities of manifestation or total discordance of findings even in monozygotic twins.

4. Hereditary factors are not always present, therefore not essential, in the etiology of so-called schizophrenic psychoses.

Studies on twins, while aiding us to discriminate be-

tween hereditary and environmental influences, tell us little of the type of hereditary behavior involved, although Rife (1938) has elaborated a statistical method which may become of service in this regard. For the exact nature of the hereditary factors involved we must of necessity turn to the study of family histories.

Here we are doomed to disappointment, for the studies of Lundborg, Witterman, Rosanoff, Oberholzer, Rüdin, Luxenburger, and others, when examined by modern statistical analysis, reveal merely that dementia praecox is apparently not dependent upon a simple Mendelian dominant nor even upon a simple recessive factor. The possibility remains, of course, that the genetic factors involved are in fact simple in nature but that their expression is so overlaid and modified by environmental influences as to mask their simplicity. The best we can do at present is to state that the probability is that dementia praecox is dependent upon several interacting genes, plus certain unknown etiologic agents of the environment.

Manic-depressive psychosis (Borrows 1828, Kahlbaum 1876, Kraepelin 1896). Turning to manic-depressive psychosis, we find that the results are similar to those for schizophrenia. In studying twins, Luxenburger found that where one twin exhibited manic-depressive psychosis, the other one did also in twenty-four out of twenty-five cases of monozygotic pairs, but in a minority of dizygotic pairs. Humm found concordance in six out of eight pairs of identicals, but in only one out of fourteen pairs of fraternals. Rosanoff and his co-workers found less striking contrasts, but report similarity in sixteen of twenty-three

monozygotic pairs and in only eleven out of sixty-seven dizygotic pairs.

The family history studies of manic-depressive psychosis are less extensive than those of dementia praecox, but the work of Luxenburger, Rüdin, Hoffman, and others indicates that the disease is inherited as a so-called irregular dominant. The irregularity of the dominance is at least partly due to unidentified environmental factors.

The psychoses just discussed are the only two which appear to have significant hereditary backgrounds. In addition, much research work has been done on epilepsy and the various types of feeblemindedness. Both from the standpoint of twins and of family histories, within the usual range of environment the genetic factor in feeblemindedness and in its counterpart, intelligence, is even more manifest and more important than in any of the conditions herewith discussed. In epilepsy the genetic factor has been considered less manifest and probably less important, although recent work with the electroencephalograph is opening up entirely new fields of research in the inheritance of this condition.

One danger in evaluating twin studies based on the comparison of identical and fraternal pairs lies in underestimating the similarity of the environments of the members of identical pairs reared together. It is to be hoped that results will eventually be recorded for mental disorders, similar to those recorded by Newman for intelligence, in identical twins separated at birth and reared apart. In such cases careful descriptions and evaluations of environments become of extreme importance. It is likewise greatly to be hoped that the sub-

sequent histories of mental diseases may be recorded for groups of children reared together in a common environment, such as an orphanage.

One thing which at present baffles the geneticist (and very probably the psychiatrist and neurologist as well) is the fact that thus far no clear-cut anatomic or physiologic classification of the mental disorders is possible. Although certain mental disorders are observed as a result of organic brain disease, or associated with various abnormal concentrations of salts or of hormones, other and similar disorders are found in the absence of demonstrable pathology or physiology. There is still some debate as to whether psychological factors not subject to definition in terms of anatomy and pathology are capable of producing mental derangements, or whether we are at present simply unable to observe the variation in structural and functional patterns within the nervous system. It is my belief that we shall eventually be able to describe mental diseases in the same precise technical anatomic and physiologic terms as we now define other diseases.

In the meantime, while we are awaiting a clear understanding of the detailed structure and function of the nervous system in its reciprocal relations with bodily organs in mental health and mental disease, we may take advantage of a suggestion offered by Parker (1938). The application of drug therapy to the various behavior disorders having become increasingly popular in recent years, the possibility is advanced of discovering the basic mechanisms responsible for the disordered states by uncovering specific therapeutic technics which are successful in dealing with those states, and then working back

in a detailed effort to describe the original mechanisms. Full experimental procedures and the necessary statistical methods for evaluating the results are given. The further suggestion is then made that inasmuch as the present admittedly inadequate psychiatric categories have failed to give consistent and unequivocal genetic results, the system of classification to be arrived at by the study of amenability to drug technic would have not only clinical and therapeutic value, but genetic value as well. This suggestion would appear to have merit, and it may be pointed out that it has precedent. For example, Gilch (1937), in a careful study of skin disease, describes several types of hereditary mechanism operating within what is apparently the same disease, and attempts a clinical distinction based on the different forms of hereditary behavior; and Allan (1939) has done the same in North Carolina for peroneal atrophy.

Suggestions of this sort, in line with modern thinking along genetic lines, point directly away from the older idea of "polymorphism," in which the assumption was made that a generally poor or weak hereditary constitution might manifest itself in any one of several abnormal mental traits. Although there have been no conclusive studies which justify the point of view of polymorphism, most authors in the field of the heredity of mental traits still make much of searching for "neuropathic taints" in the families of mentally abnormal patients.

In a summary of the genetic studies it may be said that the investigations on twins and such family pedigrees as have been carefully controlled from the standpoint of environment indicate that both genetic and environmental influences are at work in the variation in

intelligence, schizophrenia, manic-depressive psychosis, and epilepsy. In the case of intelligence and mental deficiency, most of the observed variance within the usual range of environment is probably due to genetic variation, and but little to environmental variation. In the case of epilepsy we must await further developments with the electroencephalograph. For dementia praecox and manic-depressive psychosis, while we are certain that both factors are at work, we are as yet in doubt as to the proportion of the variance to be ascribed to either influence in any given situation. Experimental procedures and statistical methods of evaluating the results of such experiments are rapidly coming to hand, however, and we should not remain in the dark much longer on these fundamental problems.

In regard to mental traits of the sort which we have been discussing, we have one clear duty. Since we are now aware that both hereditary and environmental influences may modify mental traits, we must determine as objectively as possible under what conditions it may be possible or expedient to control either or both of these influences. This involves medicine, sociology, and eugenics, and demands a concerted attack by all enlightened persons. I do not intend to discuss this point except to say that through such an attack, and only in this way, can there be available to society, for use at its discretion, detailed directions for the improvement of the mental health of our citizenry.

And now for a short glance at some nervous disorders and psychopathies in which environmental variations play but a little role and genetic variations take a prominent part.

Paralysis agitans or shaking palsy (Parkinson 1817) usually begins in the fifth or sixth decade of life. There is a degeneration of the large ganglion cells of the floor of the cerebral hemisphere. In some cases the condition may be due to inflammatory or neoplastic lesions, but the majority of cases are due to a dominant hereditary factor. The trait may skip an occasional generation, indicating that the penetrance is not complete, although this may be due in some instances to an individual dying before the disease has manifested itself.

Huntington's chorea (Huntington 1872) is characterized by involuntary twitching of the head, trunk, and appendages, progressive in form and leading to dementia. Since it develops in adult life, the normal children of an affected parent cannot be sure that they will not develop it until the reproductive age has been passed. The condition is dependent upon a dominant factor with very high penetrance and good expressivity. Nearly all the cases in this country can be traced directly back to three brothers who migrated to New England in the seventeenth century.

Heredocerebellar ataxia (Marie 1914) is characterized by ataxia, intention tremor, optic atrophy, and ocular palsies. The onset occurs in the third or fourth decade. The condition appears to be due to a dominant factor with reduced penetrance.

Friedreich's ataxia will be considered in chapter 6 in connection with the muscular atrophies.

Parenchymatous degeneration of the cerebellum or primary familial degeneration of the cerebellum (Holmes 1907, Stone 1933) is a rare disease characterized by ataxia. There is no psychosis. It develops between 30

and 40 years of age, resulting in an awkward reeling gait. It is dependent upon a dominant factor, but with somewhat reduced penetrance, so that it occasionally appears sporadically.

Juvenile amaurotic idiocy (Tay 1881, 1883, Sachs 1887) is one of the storage diseases to be described in chapter 8. It involves the storage of phosphatides in the reticulo-endothelial cells, glia and ganglion cells (see table 12). It is included here because of the striking mental defect, which is an outstanding characteristic of the condition. The onset develops within the first two years of life, and leads to mental failure, paralysis, blindness, and early death. It is dependent upon a single recessive gene, and is a good illustration of the fact that a hereditary condition need not show a direct family history. Since the children invariably die of it, parents can never have the trait, yet it will be carried along as a hidden recessive by some of the normal members of the family. This condition occurs almost exclusively in Jewish families.

Mongolism (Langdon-Down 1866). There is a small but very definite familial incidence in mongolism. There are more mongols among the relatives of mongols than among the relatives of non-mongols. Among mothers who have had mongol children, older mothers predominate, and it is found that maternal age, and not the late position of the child within the family, is the important factor. The chance of producing a mongol child rather more than doubles for each increase of five years in maternal age.

Advice to families in which mongolism is a matter to be considered might well take the form of advising early

marriage and early establishment of the family. Mongolism may be due to a dominant factor with greatly reduced penetrance, or (as has been recently suggested) to a chromosomal aberration.

Phenylketonuria (Folling 1934, Penrose 1935) is a type of imbecility in which the affected individuals excrete about a gram per day of phenylpyruvic acid, an abnormal metabolite, in the urine. The normal relatives of patients do not excrete the substance. The condition is due to a recessive factor. Thus by careful research we may gradually break up a trait like feeblemindedness into various specific clinical entities, each inherited in its own way.

Diffuse sclerosis (Schilder 1912) is a rare, rapidly progressive disease characterized by ataxia, disturbances of vision, convulsions, and mental symptoms. It appears to be dependent upon a recessive factor.

Merzbacher-Pelizaeus disease (Pelizaeus 1885, Merzbacher 1910) is a rare disease with ataxia, skeletal deformities, nystagmus and inability to stand or even to sit erect. The onset begins in the first few months of life, and the condition is fatal. It is the result of a recessive factor.

Tuberose sclerosis or epiloia (Bourneville 1880) is a severe condition, frequently fatal, in which there are many small sclerotic areas in the cortex, sebaceous adenoma of the skin, and tumors of various internal organs. Convulsions frequently occur, and mental deterioration is progressive. Death usually occurs before puberty, from tumor growth or status epilepticus. The condition has been intensively studied, particularly in England,

and is definitely due to an autosomal dominant factor with a high mutation rate.

In order to set the inherited mental traits in their proper perspective with relation to mental traits as a whole, an attempt has been made to classify the various mental characteristics. The result of this attempt is presented as table 9.

TABLE 9.—*The Mental Disorders*

(Those known to have a genetic basis are printed in capital letters.)

I. Psychoses.

A. Organic reaction types.
1. With general paresis.
2. With senile deterioration.
3. With cerebral arteriosclerosis.
4. With trauma.
5. WITH EPILEPSY (see IIA, below).
6. WITH OTHER NEUROLOGIC DISORDERS (see II, below).

B. Delirious reaction types.
1. Alcoholic psychoses.
2. Due to drugs or toxins.
3. With somatic disease.

C. Paranoid reaction types.

D. Affective reaction types.
1. MANIC-DEPRESSIVE PSYCHOSIS. Dominant, with reduced penetrance and variable expressivity.

E. Schizophrenic reaction types.
1. DEMENTIA PRAECOX. Type of heredity not fully known.

F. Primary constitutional reaction types.
1. PSYCHOPATHIC INFERIOR. Type of heredity not known.
2. MENTAL DEFICIENCY (see III, below).

G. Psychoneurotic reaction types.
1. Hysteria.
2. Anxiety states.
3. Obsessive-compulsive-ruminative-tension states.

H. Neurological disorders.
  A. Convulsive-paroxysmal disorders.
    1. EPILEPSY. Cerebral dysrhythmia may be dominant.
    2. MIGRAINE. Dominant. (See also allergies, chapter 7.)
  B. Cerebellar diseases.
    1. Acute cerebellar lesions.
    2. Dyssynergia cerebellaris progressiva.
    3. FRIEDREICH'S ATAXIA. Recessive. (See also table 10, chapter 6.)
    4. HEREDITARY CEREBELLAR ATAXIA. Dominant, reduced penetrance.
    5. PRIMARY DEGENERATION OF THE CEREBELLUM. Dominant with reduced penetrance.
    6. Olivo-ponto-cerebellar atrophy.
  C. Striatal diseases (diseases of the basal ganglia).
    1. Athetosis.
    2. Stationary status fibrosus of the striatum.
    3. Progressive status fibrosus of the striatum.
      a. Chronic progressive chorea.
      b. HUNTINGTON'S CHOREA. Dominant.
      c. General paresis.
    4. Status dysmyelinization (Hallevorden's disease).
    5. Progressive total necrosis.
      a. PROGRESSIVE LENTICULAR DEGENERATION (WILSON'S DISEASE). Recessive.
      b. Carbon monoxide poisoning.
    6. Inflammations.
      a. Encephalitis.
      b. Sydenham's chorea (St. Vitus dance).
    7. Disintegrations.
      a. PARALYSIS AGITANS. Dominant.
      b. HEREDITARY ESSENTIAL TREMOR. Probably dominant.
    8. Gross vascular lesions.
  D. Inflammatory diseases of the nervous system.
  E. Infections of the nervous system (rabies, meningitis, myelitis etc.).
  F. Neurosyphilis.
  G. Cortical defects.
    1. APHASIA. Word blindness and word deafness probably genetic.
  H. Intracranial tumors.
  I. Cerebrospinal vascular diseases (cerebral oedema, apoplexies, etc.).

J. Trauma of the central nervous system.

K. MUSCULAR ATROPHIES. (See table 10, chapter 6.)

L. BLOOD DYSCRASIAS. (See chapter 8.)

M. Exogenous toxic disorders (alcoholism, storage of metals, etc.). (See also table 12, chapter 8.)

N. Demyelinating diseases of the central nervous system.
   1. Multiple sclerosis (slight evidence of heredity).
   2. Acute multiple sclerosis.
   3. Acute neuromyelitis optica.
   4. DIFFUSE CEREBRAL SCLEROSIS OF SCHILDER. Recessive.
   5. DIFFUSE CEREBRAL SCLEROSIS OF MERZBACHER AND PELIZAEUS. Recessive.
   6. LEBER'S OPTIC ATROPHY. Almost always sex-linked, occasionally autosomal. (See also chapter 4.)

O. Developmental defects.
   1. Anencephaly. Probably some genetic basis.
   2. Cerebral diplegia (Little's disease). (See also hereditary form of spastic paralysis in chapter 6.)
   3. SPINA BIFIDA. Probably recessive.
   4. SYRINGOMYELIA. Slight evidence for heredity.
   5. Klippel-Feil deformity.
   6. Acrocephaly.
   7. MENTAL DEFICIENCY (see III, below).

III. Mental deficiency.

A. Endogenous.
   1. MORONICITY. Multiple factors for low intelligence.
   2. Imbecility and idiocy.
      a. MICROCEPHALY. Recessive.
      b. Macrocephaly.
      c. Hydrocephaly.
      d. CRETINISM. (See chapter 7.)
      e. AMAUROTIC IDIOCY. Recessive. (See also table 12, chapter 8.)
      f. TUBEROSE SCLEROSIS (EPILOIA). Dominant.
      g. MONGOLISM. Dominant with very low penetrance, or chromosomal aberration.
      h. PHENYLKETONURIA. Recessive.

B. Exogenous.
   1. Trauma.
   2. Toxins.
   3. Infections.
   4. Emboli.

4

Eye and Ear Abnormalities

An extensive list of eye abnormalities giving much evidence for the existence of genetic factors is available. As long ago as 1909 Pearson and Barrington studied the effects of environment on eye defects. They found no evidence that poverty, overcrowding, immorality, schoolwork, or other environment had any markedly detrimental effect upon the eyesight of children. On the other hand, specific types of eye defects appeared to run definitely in families.

Schools for the blind formerly had large numbers of cases of blindness due to venereal diseases, making the proportion of hereditary blindness small; but today, because of the decreased gonorrheal blindness and other blindness due to improper care at birth, the proportion of hereditary blindness is large. Most of the hereditary blindness is simple in its genetic nature.

Eye defects serve to illustrate a principle frequently met with in human heredity: the fact that a given abnormality may be in some families the result of one sort of hereditary factor (gene), in other families the result of a different sort of gene. Thus a given trait may be due in one family to a dominant factor, in another to a recessive factor, and in a third to a sex-linked recessive factor. In some cases slight clinical differences may be noted in the various genetic types; in other cases no

clinical distinctions are yet manifest, although intensive study may eventually reveal such differences.

The eye is very complicated and is important as a sense organ. Moreover, it is exceptionally open to inspection and medical examination. For this reason we know much about hereditary abnormalities of the eye.

Let us take up various examples of hereditary eye anomalies illustrating various types of hereditary behavior, and at the same time familiarize ourselves with some specific types of genic action.

Albinism is a striking trait which affects the eyes as well as other parts of the body. There is an almost complete deficiency of pigment, so that the skin is very fair, the hair white or very light, and the iris pink (because of the blood showing through) or sometimes pale blue. Photophobia regularly occurs, and there may be nystagmus and errors of refraction. Albinism is due to a recessive factor, by which is meant that the gene for albinism will produce its effect only when it is present in double dose, that is, when each chromosome of the particular pair carries the factor for albinism. If the albino gene is carried on but one of the two chromosomes of the pair, the other chromosome carrying the dominant gene for normal pigmentation, the normal gene will produce its full effect in spite of the recessive gene for albinism.

It is more convenient to use symbols for particular genes than to write out the trait involved. The word *albinism* is not particularly bothersome to write out; but we appreciate the use of symbols in dealing, for instance, with "pseudohypertrophic muscular dystrophy" or "anhidrotic ectodermal dysplasia." It is customary

to represent a dominant factor by a capital letter and its recessive allele by the corresponding small letter. In the case of albinism we may symbolize the gene for normal pigmentation by *A*, its allele for albinism by *a*. Since every individual carries his chromosomes (and therefore his genes) in pairs, it is easy to see that individuals may be of three sorts in regard to the factors for albinism. A person could be of the genotype *AA*, in which case he would be normal and would not even carry a hidden factor for albinism. Such a person is said to be homozygous for the gene *A*, and most persons in the world are of course of this genotype, since the gene for albinism is rare. Again a person could be of the genotype *Aa*, heterozygous for albinism, but appear phenotypically normal. Finally, a person could be of the genotype *aa*, homozygous for the gene *a* and therefore an albino individual.

Persons of the genotypes *AA*, *Aa* and *aa* will be in the relative proportions of p^2, 2pq and q^2, respectively, in the general population, provided random mating occurs in regard to albinism. In this mathematical relation $p + q = 1$, and q is the frequency of the recessive gene. Practically, this simply means that the proportion of heterozygotes (carriers) to those showing the recessive trait will vary from trait to trait, depending upon the frequency of the trait in the population. For a recessive trait which occurs in one out of a million of the population, the carriers will be about two thousand times as frequent as those who show the trait. If the trait occurs in one out of a thousand, carriers will be sixty times as common as affected persons. If the trait occurs in one out of a hundred, carriers will be only eighteen times as

common as affected individuals. For a trait occurring in one out of six, there will be three carriers to every affected person, and so on.

Returning to albinism, we see that a person, to show the trait, must be of the genotype *aa*. Since a person receives one of each pair of chromosomes (and therefore one of each pair of genes) from his father, the other from his mother, it follows that each of the parents of an albino must have been *Aa* or *aa*. Neither one could have been *AA*. Since albinism itself is rare (something less than one in ten thousand), the parents of an albino will nearly always be normal, but heterozygous. Albinism therefore will "skip generations" in inheritance, and this is characteristic of a trait dependent upon a recessive factor.

Figure 1 presents a family history of albinism. Recessive traits such as this are diagnosed by several

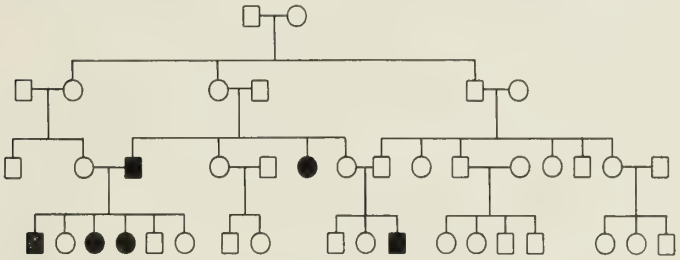

Fig. 1.—A family history of albinism. Squares represent males, circles females. Solid squares and circles indicate albino individuals.

criteria. First, they often appear when neither parent shows the trait, as has just been mentioned. This is the so-called "familial" occurrence so often mentioned in medical literature. Second, if the trait is at all rare, it will be found that the proportion of consanguinity among

the parents is higher than that found in the general population. This is due to the fact that even heterozygotes are relatively rare, but a heterozygote who marries a cousin may very well be marrying another heterozygote. In the case of albinism this criterion is met, since the consanguinity among the parents of albinos is about twenty times as high as that found in the general population.

Third, when two people showing the recessive trait marry, all their children should show the trait. This criterion is often difficult to meet in a rare trait, and is sometimes impossible of fulfillment where, for instance, the trait is lethal. We must often depend upon the first two requirements, plus certain refined statistical technics which are beyond the scope of these lectures. In the case of albinism, however, several cases of the marriage of two albinos are on record, and no offspring other than albinos have been produced. We can therefore state that albinism depends upon a recessive gene.

Turning now to *high myopia*, we find that some families fulfil the requirements for the dependence of the trait upon a recessive gene. In these cases it is usually found that there is undue length of the globe. In other families, however, the myopia is correlated with excessive curvature of the cornea, and here we often find evidence that the factor for high myopia is dominant. The inheritance of a trait dependent upon a dominant factor is somewhat different from that of a trait produced by a recessive factor. Symbolizing the gene for dominant myopia by *M* and its recessive allele for normal vision by *m*, a myopic person could be *MM* or *Mm*, while a normal person must be *mm*. In such a case every myopic person

would be expected to give the factor *M* to at least half of his offspring; and conversely, every myopic person would have received the factor *M* from at least one of his parents, who would thus be myopic.

Such a trait, then, does not skip generations, but runs directly down through a family (figure 2). This type

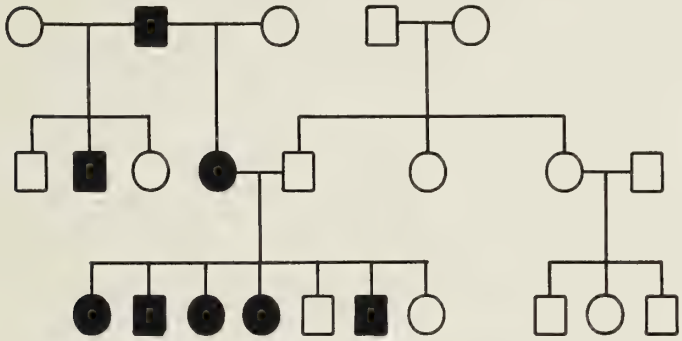

Fig. 2.—A family history of a dominant form of high myopia.

of transmission is what the physician usually speaks of as "hereditary" in contrast to recessive or "familial" inheritance. Actually, of course, both are examples of hereditary transmission.

Hyperopia or farsightedness is a condition in which the axis of the globe is too short so that the rays are focused behind the retina instead of on it. Hyperopia is frequently due to a dominant factor, but occasionally to a recessive gene.

Optic atrophy or Leber's disease, in which some peripheral vision usually remains, presents a third type of genetic behavior. The usual type of heredity in this disease is on the basis of a sex-linked recessive factor. Sex-linked factors are those factors which are located on

the X-chromosome of the sex pair (X and Y), in contrast to those factors previously discussed, which were located on one or another of the autosomes. The autosomes include all chromosomes except sex chromosomes.

Using *O* for normal vision and *o* for optic atrophy, and considering these factors as located on the X-chromosome but not the Y-chromosome, one sees that women could be of any one of the three usual genotypes, *OO, Oo* (normal), and *oo* (optic atrophy), while men could be of only two genotypes, *O*Y (normal) and *o*Y (optic atrophy).

This arrangement of factors will result in a mode of transmission different from those previously discussed. A man with optic atrophy will be of the genotype *o*Y, and will pass on the gene *o* in half his sperms and the blank Y-chromosome in the other half. Since the sperms carrying the Y-chromosome will result in sons when an egg is fertilized, it follows that a man cannot transmit the factor for optic atrophy to his sons, but only to his daughters. Since these daughters will usually receive from the mother an X-chromosome carrying the normal factor *O* (because the recessive gene *o* is rare), they will be normal but heterozygous. In the next generation they will give the recessive factor *o* to half their sons, who will therefore have optic atrophy because the other chromosome of the pair will be the Y-chromosome derived from the father.

It follows that there will be in the general population more men than women with optic atrophy. A man receiving a gene *o* must show the atrophy because the other chromosome, the blank Y-chromosome, cannot carry the dominant factor to prevent the recessive *o* from acting. A woman, however, who receives the recessive *o* on one

X-chromosome will most probably receive the dominant *O* on the other, and will therefore be normal. A typical family history involving the sex-linked optic atrophy is shown in figure 3.

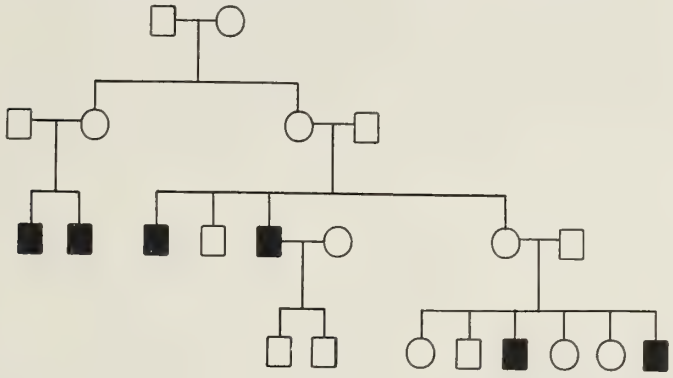

Fig. 3.—A family history of Leber's optic atrophy, illustrating the inheritance of a trait dependent upon a recessive sex-linked gene.

A sex-linked recessive trait can, however, appear in women if the father shows the trait and if the mother is a carrier. For example, a man with optic atrophy of the genotype *o*Y, marrying a "carrier" woman of the genotype *Oo*, may have a daughter with optic atrophy who received the gene *o* from each parent. Such an occurrence is shown in figure 4.

Advice to families in the case of a sex-linked trait is important. The men in the family who are free from the trait cannot possibly transmit it, and may safely marry. The normal women in such families, however, may very well carry the recessive factor, which could produce the trait in some of their sons. The daughters of an affected man are *all* carriers. The sisters of an affected man whose father was normal have a fifty-fifty chance of being car-

riers. The nieces of an affected man have one chance in four of being carriers, etc. The affected men themselves will of course transmit the factor to all their daughters, who ordinarily will not show the trait but will transmit the factor to half their sons who will show it, and half their daughters who probably will not show it. An affected man cannot transmit the factor to his sons. Dominant or recessive forms of optic atrophy are occasionally encountered.

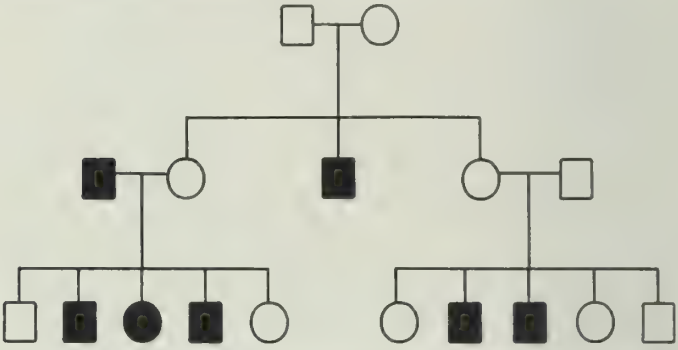

Fig. 4.—A pedigree illustrating the circumstances under which a sex-linked trait may appear in a woman. The trait is optic atrophy.

Aniridia, the absence of the iris, is usually dependent upon a dominant factor. A girl in one of the schools for the blind, suffering from aniridia, was about to elope. Some of her friends persuaded her to consult a medical geneticist. Although her father and grandmother had both had aniridia, she was amazed to learn that the trait would be expected to show up in half her children, both boys and girls.

Nystagmus, continual rolling movements of the eyeball, often accompanied by movements of the head, may sometimes be due to brain lesions, or to a tumor or cyst.

Many cases, however, show a clear dominant heredity. In some families there is a sex-linked type of nystagmus, and in these families there are no accompanying movements of the head.

Cataract usually shows a dominant type of inheritance. However, the condition occasionally fails to appear even though the person inherits the factor for it. Here we encounter another principle of genetics, the phenomenon of *penetrance*. If a dominant gene always produces its effect in an individual who inherits the gene, we say that it has complete penetrance. If, however, some persons may have the dominant gene and yet not show the trait, we say the gene has reduced penetrance. Ideally the amount of penetrance should be stated for each dominant gene. Wherever possible this will be done in these lectures, but much more research is needed before our knowledge on this point can be complete. Where penetrance is reduced, the cause may be genetic (the residual heredity) or environmental. Obviously much very practical research is possible along this line. This point will be further discussed in chapter 7.

In addition to the penetrance of a gene, we also speak of its *expressivity*. By this we mean the variation in expression which the trait may show even though it is fundamentally produced by a single gene. Again the variable expressivity will be caused sometimes by the modifying effects of other genes, sometimes by environmental factors. For examples of expressivity, see hemolytic icterus and erythroblastosis to be discussed under the anemias in chapter 8.

Glaucoma, in which an intraocular tension leads to atrophy of the retina and blindness as a result of block-

age of the lymph drainage of the eye, is of course environmental in many cases. In other cases, however, there is clear evidence of a dominant factor with high penetrance.

Retinitis pigmentosa, involving atrophy and destruction of the retina and deposition of pigment with resulting blindness, is found to be recessive in some families, dominant in others, and sex-linked in still others. Advice to families must take into account the family history of the individual patient.

Ptosis, the inability to lift the eyelids, may of course be due to injury to the lid, or paralysis of various nerves, but these environmental causes usually produce a unilateral ptosis. Aside from these are many cases of bilateral ptosis, and these are generally the result of a dominant hereditary factor.

As a general principle it may be stated that when a trait which could be bilateral is found in a unilateral condition, it is most probably due to environment; but when it is found in a bilateral condition, it is most probably the result of a genetic change.

Blue sclerotics represents a condition involving widespread failure of development of connective tissue. The sclera are thin, translucent, and bluish. The scleral coat is only one third of its normal thickness. There is a marked fragility of the bones, resulting in many fractures, even up to fifty or sixty in an affected person. The condition is the result of a dominant gene.

Color-blindness of the red-green type is dependent upon a sex-linked recessive gene. There are as a result more color-blind men than color-blind women, since a color-blind son may be the offspring of a normal father and a normal (though heterozygous) mother, while a

color-blind daughter must have a color-blind father and a heterozygous mother. Actually the situation is complicated by the fact that heterozygous women are very occasionally slightly color-blind. A further complication results from the existence of several alleles for varying types of color-blindness.

Other eye anomalies may be briefly listed according to the type of inheritance involved:

Dominant: ectopis lentis, lagophthalmus, epicanthus, distichiasis pterygium, arcus juvenilis (embryotoxon).

Recessive: cryptophthalmus, hydrophthalmus, keratoconus.

Sex-linked recessive: megalocornea, day-blindness.

Dominant in some families, recessive in others: coloboma iridis, corneal opacities, strabismus, ophthalmoplegia, astigmatism.

All three types of inheritance: retinal detachment, microcornea, microphthalmus, night-blindness.

Ear Abnormalities

Deaf-mutism is the result of a recessive genetic factor, but there are two different pairs of factors concerned, the recessive of either of which may produce deafness. If we symbolize these two pairs of factors by *D, d* and *E, e,* a normal person must have both dominant factors, and could be of the genotypes *DDEE, DdEE, DDEe,* or *DdEe.* A deaf person could be *DDee, ddEE,* or *ddee.* The fact that *ee,* for example, results in deafness, even though the person may have the factors *DD* for normal hearing, is the result of *epistasis* of *e* over *D.* Epistasis is the same relation between factors of two different pairs as dominance is between the two factors of one pair.

The result of this type of inheritance is that two con-

genitally deaf parents will not always have deaf children. If the parents are both *DDee*, for example, all the children will be deaf, but if one parent is *DDee* and the other *ddEE*, the children will all be *DdEe*, and thus will be hearing individuals (figure 5). It would be desirable

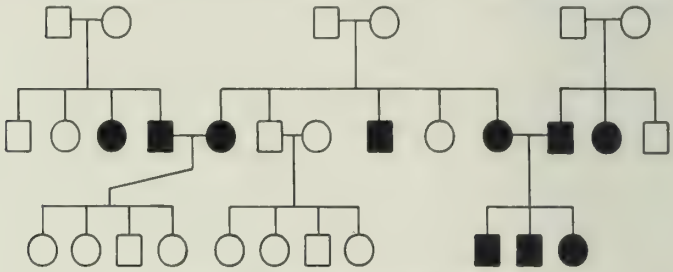

Fig. 5.—A pedigree of deaf-mutism.

to find a phenotypic distinction between the two pairs of factors, so as more correctly to advise prospective marriage partners. Audiometer records do not bear out the possibility that one gene removes hearing from all but the upper register, while the other removes hearing from all but the lower register. The best lead at present indicates that one gene results in atrophy of the auditory nerve, the other in atrophy of the cochlea.

Otosclerosis is progressive deafness beginning at about 30 years of age but not usually causing complete deafness. The inheritance is somewhat complicated. Davenport suggests that otosclerosis is the result of the interaction of two dominant factors, one an autosomal factor and the other sex-linked.

Labyrinthine deafness, in which the auditory nerve elements degenerate and are replaced by connective tissue, beginning in the fifth decade, is apparently dependent upon a dominant factor.

5

Abnormalities of the Skin

Many skin diseases are the result of infections to which everyone is probably susceptible if he comes into proper contact with the causative agent. Many skin abnormalities, however, are definitely the result of specific genetic factors.

Cockayne, in his excellent book on skin conditions, lists about eighty abnormalities which are the result of specific dominant factors, twenty which depend upon recessive factors, seven which are due to recessive sex-linked factors, and three which apparently involve dominant sex-linked factors. In addition, there are four conditions, the factors for which are carried on the Y-chromosome. These last four will be considered in chapter 10. In this chapter we may consider some of the interesting skin anomalies which are the result of genes of the types already familiar to us.

Psoriasis (figure 6) involves the formation of numerous circumscribed reddish-brown inflammatory areas covered with scales, usually on the arms, legs and neck, beginning at puberty or adolescence. The etiology is unknown, some considering it a genetic susceptibility to a parasitic fungus, others holding that it is allergic or toxic. Whatever the etiologic basis, it seems to be genetic. There is a dominant form in some families, a recessive form in others, indistinguishable clinically.

A practical example of the application of the knowledge of genetics to advice in regard to this condition is

Fig. 6.—Psoriasis.

furnished by the case of a young medical student. He had married during the summer which was spent in clinical work at a medical school. Not until the Christmas vacation did he have an opportunity to take his bride to his home, considerable distance away. There she met many members of his family and noted that various relatives suffered from a severe form of psoriasis, so unsightly as to prevent the women and girls from wearing low-necked or sleeveless gowns.

At this time the young bride was pregnant, and she became worried for fear her baby would have psoriasis. It preyed on her mind to such an extent that she was in danger of a psychosis. The young man came to us in despair. We charted his family history, noted that the psoriasis in this family was clearly the result of a dominant factor with high penetrance, and that the young man in question was free from it (figure 7). We were thus able to assure the bride that her baby, represented

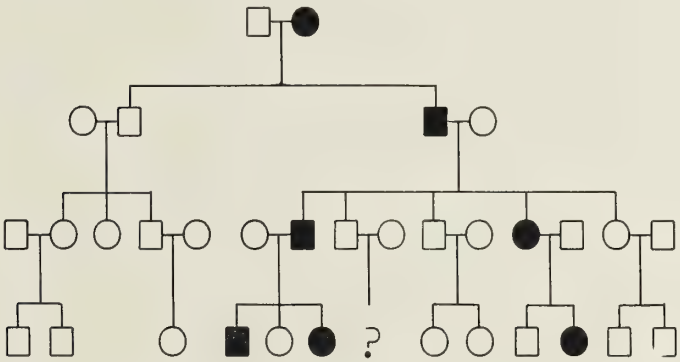

Fig. 7.—A pedigree of psoriasis dependent upon a dominant factor The question mark indicates an unborn child for whom a genetic prognosis was requested. See text.

by the question mark in figure 7, would almost certainly not develop psoriasis.

A contrasting pedigree of recessive psoriasis, taken from our records, is presented in figure 8. Note that in

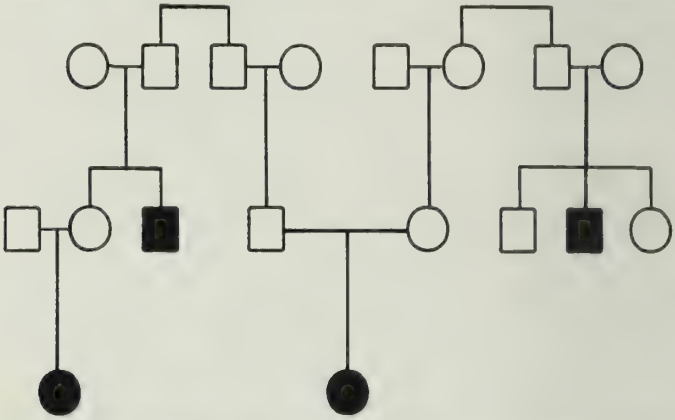

Fig. 8.—A pedigree of psoriasis dependent upon a recessive factor. Contrast this with figure 7.

the case of a recessive factor, the trait is much more likely to show up in the collaterals than in the immediate ancestors or in the direct descendants.

Epidermolysis bullosa (Goldschneider 1882) is of several sorts. In all of them blisters appear on the skin, chiefly of the feet, hands, knees, and elbows, as a result of slight friction or abrasion (figure 9). In the simple form the blisters are in the epidermis, and usually heal without leaving scars. The nails are unaffected. This type is dependent upon a dominant factor.

In the dystrophic forms the bullae are deeper, between the epidermis and the corium, and leave permanent scars. Likewise scarring and atrophy of the nails occur. There are two clinical forms of the dystrophic type, differently

inherited. In the dominant form the teeth and hair are unaffected, but the nails are thickened or distorted, and epidermal cysts may occur. The condition is not fatal and may improve in later life.

In the recessive dystrophic form the teeth are abnormal and deficient in number, the skin is frequently cyanotic, the nails are invariably absent or deformed, and the conjunctiva and cornea may be affected. The bullae, in addition to the regular places, may be formed in the mucous membranes of the nose and mouth, the pharynx, larynx, bronchi, and esophagus. The condition is usually fatal in infancy or childhood. The recessive factor for this condition is incompletely sex-linked, a phenomenon which will be discussed in detail in chapter 10.

Keratosis includes several defects, some of which are as follows:

Keratosis palmaris et plantaris. The formation soon after birth of cornified areas on the soles of the feet and the palms of the hands, which are often marked off from the normal areas by a thin bluish line. The usual form is dependent upon a dominant gene, but aberrant forms with correspondingly different inheritance have been recorded.

Keratosis follicularis (Jadassohn and Lewandowski 1906, Bettman 1909) involves the formation of horny growths on various parts of the body, with a peculiar cellular degeneration of the hair follicles and the destruction of the oil glands in affected areas. The sweat glands are, however, normal. The condition is due to a dominant factor.

Ichthyosis (Gaskoin 1877-8) is another term covering

several distinct abnormalities, some of which are as follows:

Ichthyosis fœtalis. The skin is enormously thickened and split into plates of varying sizes by deep fissures. The neck is short and broad and the chin is bent towards the chest. The general appearance is very abnormal, and the infants live only a few hours. In many of the cases consanguinity of the parents is noted, and the abnormality is apparently the result of a recessive lethal gene.

Ichthyosis congenita is similar to the foregoing anomaly, but the fissures occur shortly after birth instead of before. The two conditons may very well be the variable expression of the same recessive gene. This form is not necessarily fatal.

Ichthyosis vulgaris is a condition in which the skin is dry and covered with small dense scales or horny flakes which are continually being shed. The onset is in early infancy, and it is progressive up to the age of about ten. It is dependent upon a dominant gene with variable expressivity ranging from severe cases represented by the "porcupine men" of the circus to very inconspicuous and mild cases.

Monilithrix is a trait in which the hair is peculiarly beaded, having constrictions at regular intervals with spindle-shaped thicker regions between. The onset is in early childhood, and involves keratosis of the follicles and alternating periods of growth and inactivity of the hair. Whenever the hair reaches a length of an inch or even less, it breaks off at one of the constrictions, leaving the patient with a sparse covering of short twisted broken hairs with no lustre. The trait is dependent on a dominant gene.

Anhidrotic ectodermal dysplasia (Widderburn 1838) involves the total absence of sweat glands. Usually there are also small size and delicacy of constitution and total absence or deficient number of teeth, which, if present, are conical. There is scanty fine hair, often absence of the lachrymal glands, and there may be chronic rhinitis with subsequent loss of the sense of smell. The patients suffer tremendously from heat, and must in hot weather immerse themselves in water or keep their clothing wet. The usual form of this anomaly is due to a sex-linked recessive factor, but a somewhat different dominant form is known as well.

An interesting example of the practical value of a knowledge of the genetic nature of this condition is contained in a report by Macklin. There was brought to a physician a child whose skin was very dry, who had sparse hair and but one tooth. The physician diagnosed it as hypothyroidism and placed the child on thyroid medication. This not only failed to help the patient, but caused even more discomfort. Finally, after a great deal of this treatment another physician was consulted, who noted that the mother and several other members of the family also had dental aplasia. On this basis the condition was identified as the dominant form of ectodermal dysplasia, and thyroid administration was stopped, since this had been as harmful a type of therapy as could well have been devised. Here the family history gave the clue to the correct diagnosis.

Hypotrichosis, the partial or complete lack of hair due to errors of development, includes several genetic anomalies, some of which are discussed herewith.

Hypotrichosis universalis involves the complete absence

of hair on the body at birth or soon thereafter. It is due to a dominant factor.

Hypotrichosis et dystrophia unguium involves dystrophy of the nails, with abnormal scantiness of the hair. The eyebrows are absent, and the eyelashes are few or absent. A dominant factor is responsible.

Pattern baldness is dependent, when not the result of disease, upon a sex-influenced factor. By this we mean a factor located upon an autosome, but being dominant in males and recessive in females. Thus bald men will have on the average one half of their sons bald, but their daughters will not be bald unless the mother comes from a family with baldness. Men may become bald, if neither parent is bald, by inheriting the factor from their mothers, in whom it was recessive, although in the men it acts as a dominant and shows up. Baldness occurs in about 7 per cent of women, but in more than 40 per cent of men.

Hypertrichosis, involving the persistence and excessive growth of the lanugo hair associated with imperfect development of the teeth, is dependent upon a dominant factor. The condition becomes noticeable at the age from 2 to 7 years, and the lanugo hair continues to develop until the entire body is covered with it, 4 to 10 inches long. The mutation has apparently independently arisen several times, since in addition to six family groups four isolated individuals are known. The famous JoJo, the "dog-faced man" of the circus, was one of these.

Teeth. There are many families in which genetic absence or deformity of teeth occurs. Some of these have already been mentioned in connection with other ectodermal anomalies. Supernumerary teeth are inherited on

Fig. 9.—Epidermolysis bullosa.

the basis of a dominant factor. The absence of upper incisors seems to be sex-influenced in the same manner as baldness.

Finger prints are hereditary, but no simple law of inheritance has as yet been found to apply. The finger prints of relatives are more similar than those of unrelated individuals. The finger prints of the two members of a pair of identical twins are not, however, identical, nor are they exact mirror images, indicating the influences of fortuitous stretching of the skin during development.

Von Recklinghausen's disease or neurofibromatosis (Von Recklinghausen 1882) involves skin lesions and lesions of the peripheral nerves accompanied by pale brown patches of pigmented skin (figure 10). It begins in childhood and is progressive. The lesions tend to become sarcomatous in about 15 per cent of the patients. The disease is the result of a dominant gene, which at first was thought [illegible] netrance. Better acquaintance with [illegible] icates that the penetrance is very [illegible] ressivity is variable, including cafe- [illegible] ıcutaneous tumors, pachydermatoco- [illegible] euromatosa, fibroma molluscum, and [illegible] (figure 11).

Mongolian sp [illegible] t striking condition, involving an i[illegible] bluish spot on the lumbar region of newborn children. The spot ranges in size from that of a pea to that of an orange, and usually fades out in childhood. It is almost universal in Mongolians, frequent in the black and brown races, and rare in whites (about one in 200). It does not indicate Mon-

golian ancestry. It appears to be due to a dominant factor.

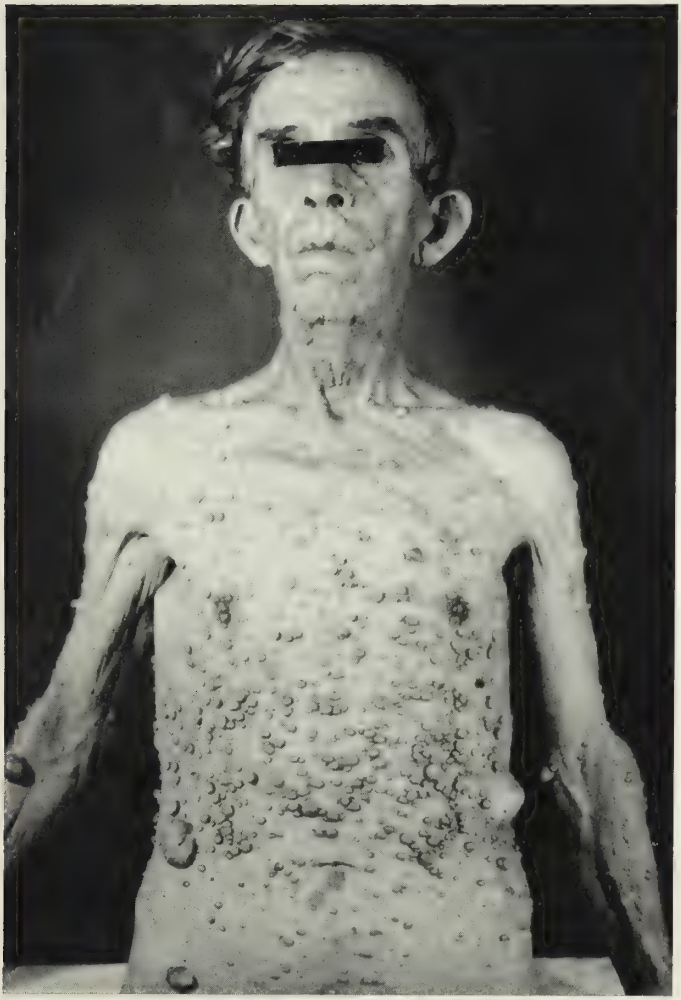

Fig. 10.—Neurofibromatosis (Von Recklinghausen's disease).

Skin color depends upon several pairs of multiple factors. When one parent is of pure white ancestry and the other is "pass-for-white," the children are not darker than the darker parent, although this fact spoils the effects of certain novels and short stories.

Fig. 11.—A plexiform neuroma, one of the manifestations of Von Recklinghausen's disease.

6

Skeletal and Muscular Abnormalities

Many interesting and important anomalies of the skeletal and muscular systems have a genetic basis. A few of the more important will be chosen for discussion, especially those which illustrate principles of genetics, principles of diagnosis, or principles of prognosis.

Brachydactyly. Incomplete development of the middle phalanx of the digits (other than the thumb and big toe). The middle phalanx is a shortened malformed bone, more or less fused with the base of the terminal phalanx; or it may be absent altogether. The long bones of the limbs may be shortened, leading to a deficiency in stature. The condition is dominant, with complete penetrance and perfect expressivity.

Minor brachydactyly (Mohr and Wriedt 1919). The middle phalanx is shortened only in the index finger and second toe. It is dominant, with what appeared at first to be lowered penetrance. Careful measurements, however, show that the penetrance is complete, but the expressivity is poor in some cases. Careful measurements were taken of the index and ring fingers of the same hand on the members of a pedigree of minor brachydactyly and expressed in the form of a ratio. These were compared with measurements from several hundred controls. In persons who transmitted the trait without

showing it, the ratio was lower than in any of the controls.

This family also illustrates the principle that the homozygous dominant (which we seldom have an opportunity to see in a rare trait) may be much more severe than the heterozygote. In this family, two individuals with the trait married, and the homozygous dominant was very abnormal and lethal.

Polydactyly is dominant in the white race, but with low penetrance in some families, and poor expressivity, varying from well-developed extra digits to nodules. There is a recessive type in Negroes (Snyder 1928).

Symphalangy, a fusion of the proximal and middle phalanges, is dependent upon a dominant factor.

Syndactyly, in which two or more fingers or toes are grown together, is frequently the result of a dominant factor, but is sometimes sporadic. The sporadic cases may be new mutations.

Lobster claw, or split hands and feet, is a rare condition usually inherited on the basis of a dominant factor. Keeler records the case of a man with lobster claw who was assured by his physician that his condition could not be transmitted, but who subsequently had two lobster-clawed children.

Absence of the patella has been recorded as due to a simple dominant factor.

Multiple cartilaginous exostoses (figure 12) involve cartilaginous growths on the bones. The inheritance is according to a dominant gene, but with only about 70 per cent penetrance. Macklin cites a case of a child who had a bony lump on its arm. X ray revealed a growth, and a diagnosis of sarcoma was made. Operation was

Fig. 12.—Multiple cartilaginous exostoses.

advised, but the parents were unconvinced, and sent the child to another city, where another physician showed other beginning growths. A diagnosis of multiple exostoses was made when it was found that the father also had small growths of the same sort. An acquaintance with this hereditary disease and with the fact that it was inherited led to the correct diagnosis and saved the child's arm.

Congenital dislocation of the hip is dependent upon a dominant factor with reduced penetrance.

Dwarfism. Measurements of height made upon a large unselected group of persons will give rise to a normal curve of stature. Some people are very short because they have all or most of the multiple factors for shortness. Others, beyond the normal range, are pathological entities. The situation is similar to that in intelligence, where beyond the normal curve of mental ability are pathological entities, such as microcephaly and mongolism. The pathological entities included in dwarfism are several, some of which may be individually discussed.

Among the causes of dwarfism is *rickets*, which may be considered largely if not entirely environmental, that is to say, nongenetic. A common cause is *cretinism*, which involves an interaction of environment (iodine deficiency) and genetic factors. Dwarfism may be due to *ateleiosis*, where the skeleton remains in the type found in childhood. Ateleiosis is clearly hereditary, but no simple mechanism of transmission has been proved. Tom Thumb married another midget and had a normal child. *Achondroplasia* may be the cause of dwarfism (figure 13). Here there are an arrest of development and a premature bony union. This is the type frequently

Fig. 13.—Achondroplasia. These two sisters show a recessive form of the condition, as borne out by their pedigree in figure 14.

found in side shows. Caesarian section has permitted women dwarfs to undergo successful childbirth, adding to the genetic data. Achondroplasia is usually dominant, but Allan has found evidence for the existence of a recessive type (figure 14).

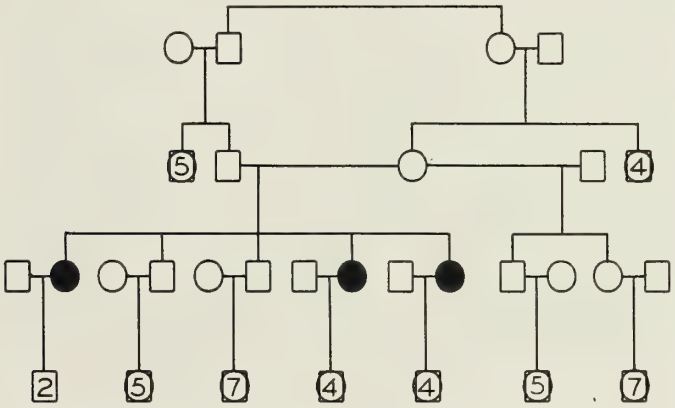

Fig. 14.—A pedigree of recessive achondroplasia.

Morquio's disease or osteochondrodystrophy (Morquio 1929) results in varying degrees of dwarfism. It is a developmental disease of the skeleton, characterized by osseous dystrophy and deformities of the trunk and extremities. The deformities become progressively worse,

Fig. 15.—A brother and sister with Morquio's disease. There were eight other children, all normal.

but the condition is not usually fatal. It appears to be dependent upon a recessive factor (figure 15).

Spina bifida is apparently recessive, although the frequent occult nature of the condition makes genetic analysis difficult. Macklin records the case of a man with an ulcerated corn. Several physicians had failed to give him relief. Finally, a neurologist who had treated the man's two brothers for marked trophic lesions due to spina bifida proved by X ray that the ulcerated corn was a similar trophic condition due to the same cause. The knowledge of the family history gave the clue to the diagnosis.

Club foot has an undoubted genetic basis, but no clear type of inheritance is known for it as yet. It may be due in some instances to environmental causes such as unfavorable position in utero or foetal membranes which are too small. The consanguinity of parents is much higher in club foot than is found among the general population, indicating a recessive type of inheritance.

Hare lip and cleft palate may be recessive, but the pedigrees are rather fragmentary. The fact of heredity is not any too clear in these conditions.

Hypospadias, in which the aperture of the urethra is on the anterior surface of the penis at varying distances from the extremity, appears to be due to a dominant factor with reduced penetrance.

The Muscular Atrophies

Many of the muscular atrophies (see table 10) have a clear simple hereditary basis. The atrophies may be myopathic, in which the muscles are primarily involved, or myelopathic,

TABLE 10. *The Muscular Atrophies*

(Those known to have a genetic basis are printed in capital letters.)

I. Idiopathic.
  A. Myopathic.
    1. Myasthenia gravis.
    2. AMYOTONIA CONGENITA. Recessive.
    3. FAMILY PERIODIC PARALYSIS. Dominant with reduced penetrance.
    4. PROGRESSIVE MUSCULAR DYSTROPHY (PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY). Commonly sex-linked recessive; some cases due to autosomal recessive.
    5. MYOTONIA CONGENITA. Dominant.
    6. DYSTROPHIA MYOTONICA. Dominant.
  B. Myelopathic.
    1. Progressive spinal muscular atrophy.
    2. Amyotrophic lateral sclerosis.
    3. HYPERTROPHIC NEURITIS. Probably recessive.
    4. PERONEAL ATROPHY. Dominant, recessive, sex-linked recessive.
    5. INFANTILE MUSCULAR ATROPHY. Recessive.
    6. FRIEDREICH'S ATAXIA. Dominant, recessive.
    7. HEREDITARY SPASTIC SPINAL PARALYSIS. Recessive, occasionally dominant.

II. Secondary.
  A. Disuse.
  B. Trauma.
  C. Tabes dorsalis.
  D. Neuritis (virus, bacterial, toxic, vitamin deficiency, etc.).
  E. Poliomyelitis.
  F. Electrical injury.

in which the spinal cord is also involved. Among the myopathic forms are the following.

Amyotonia congenita (Oppenheim 1900). Extreme flaccidity of muscles: the opposite of myotonia. The limbs are most affected, the trunk next, and the face least of all. There is a condition of general weakness but little or no true atrophy. About 25 per cent die in the first year of the disease, which starts during the first year of

life. The survivors tend towards slow amelioration, but never attain normal muscular power. The condition is dependent upon a recessive factor.

Family periodic paralysis (Cavaré 1853) involves attacks of flaccid paralysis, occurring at irregular intervals, lasting from a few hours to two or three days. The onset occurs at puberty. It is dependent upon a dominant factor with slightly reduced penetrance. There may be, in addition, a recessive form.

Progressive muscular dystrophy or pseudohypertrophic muscular dystrophy (Duchenne 1860, Erb 1883, Landouzy 1884, Gowers 1902, Spiller 1913) involves proximal atrophy combined with pseudohypertrophy, especially of the calves of the legs. The onset begins during the first decade, and the condition is progressive. The prognosis is hopeless, death usually occurring during the second decade. The common type is sex-linked, and the condition is confined to boys. There is, however, a recessive type occurring in both sexes. There are about 175 living dystrophies on record in North Carolina, all of whom are doomed to early death (figure 16).

Advice to families in these cases is practical and important. When the girls in the sex-linked families have spent their childhood and adolescence caring for crippled brothers, getting up at night to turn them over and attend to them, they do not want to spend the rest of their lives caring for crippled sons. Yet one half of such girls will be expected to have crippled sons, no matter whom they marry.

Myotonia congenita (Thomsen 1870) is a condition in which muscles which are used after being in repose pass into a condition of extreme contraction which cannot be

voluntarily relaxed until after an appreciable period of several seconds. The onset occurs in earliest childhood, but the symptoms may not be noticed until puberty. The condition is not fatal and is dependent upon a dominant factor.

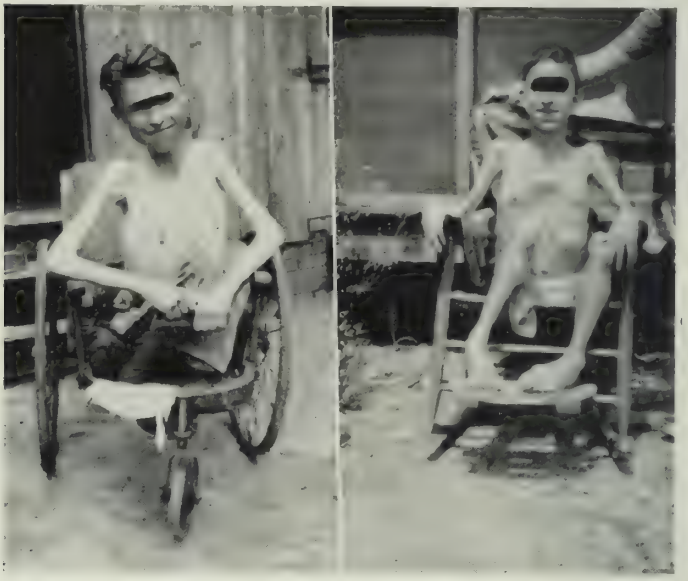

Fig. 16.—Two boys with pseudohypertrophic muscular dystrophy of the sex-linked recessive type.

Dystrophia myotonica (DéLéage 1890) is a general dystrophic disorder which may involve myotonia of the hands, legs, and chewing muscles. The onset is usually between 20 and 35, and there is a progressive general muscular atrophy with drooping head and curious gait. There is wide variation in manifestation from severe to very mild. Patients usually die before 50 in exhaustion

states. The condition is due to a dominant gene with good penetrance but poor expressivity.

In addition to the myopathic muscular atrophies just discussed, there is a series of myelopathic forms, involving the central nervous system. Among these are the following.

Hypertrophic neuritis (Dejerine-Sottas 1893). Here there is an enlargement of the peripheral nerves, with retardation of sensations and ataxia of all four limbs with atrophy. The onset occurs in the first or second decade as a rule, but may be later. It appears to be caused by a recessive factor.

Peroneal atrophy (Charcot-Marie 1886, Tooth 1886) is a localized atrophy of the lower legs and forearms. Later other muscles of the arms and legs may become involved. Dominant, recessive, and sex-linked recessive types are known. In the dominant form, the onset is in the second decade. The individuals become lifelong cripples with much difficulty in walking or in working with the hands. In the recessive type the onset is before the age of 10, and the patients usually die early. In the sex-linked form the onset is also early, but the condition is not apt to be so severe as in the recessive type.

More than one thousand cases of peroneal atrophy are on record in North Carolina, involving more than one hundred family trees, ranging from five to sixty affected members a family, according to Allan. This disease causes much sorrow in the home and much loss of work (figure 17).

Infantile muscular atrophy (Werdnig 1890, Hoffman 1891) is a progressive atrophy beginning in the trunk and the legs and sometimes leading to complete paral-

ysis. The onset is in the first few months of life, and death occurs within a year or two, the result of a recessive lethal gene.

Fig. 17.—Peroneal atrophy.

Friedreich's ataxia (Friedreich 1863) is included here because muscular atrophy, fibrillation, and cramps are commonly associated with the ataxia, speech defect, and so on. The onset is during childhood, and the ataxia spreads slowly until the patient is unable to walk. There is a degeneration of the dorsal roots of the spinal cord.

The condition is dominant in some families, recessive in others. See tables 9 and 10.

Hereditary spastic spinal paralysis (Erb). The hereditary form of spastic paraplegia is not common. The age of onset is from 6 to 30 years. There is degeneration of the pyramidal tracts with exaggerated reflexes and later weakness. It is usually recessive, occasionally dominant.

7

Diatheses and Susceptibilities

There is evidence for the genetic or partial genetic basis for a group of miscellaneous diatheses, which may now be discussed.

Diabetes mellitus may in some instances be caused by external influences, such as emotional states (fear, pain, sorrow) which produce vaso-motor disturbances that may impair the normal function of the islands of Langerhans, or it may be the result of syphilis or other causes. In the majority of cases, however, heredity is the determining cause (see table 12).

Pincus and White indicate a simple recessive inheritance of diabetes mellitus on the basis of many hundred family histories from the Deaconess Hospital records in Boston. On the other hand, Levit and Pessikova present convincing evidence for the transmission of this condition as the result of a dominant gene with reduced penetrance.

The differentiation between a dominant gene with low penetrance and a recessive gene is not easy, and can be accomplished only with reasonably large and unbiased samples. In the case of a recessive gene it will be recalled that the proportion of affected brothers and sisters of an affected patient will be much greater than the proportion of affected parents or of affected children. Moreover, if the recessive gene is at all rare, there will most probably

be an increased rate of consanguineous matings among the parents.

In the case of a dominant gene it will be recalled that with full penetrance the proportion of affected brothers and sisters of an affected patient will be approximately one half. Likewise affected patients will have parents and children one half of whom are affected. Only one quarter of the grandparents, grandchildren, uncles, aunts, nephews, and nieces will be affected, and only one eighth of the first cousins.

Now suppose that the penetrance of the dominant gene is much reduced. The foregoing proportions will similarly be reduced, and the character will be sporadic and may appear to be recessive; but the proportions referred to will keep their relative ratios, and these ratios are different from those to be found in recessive inheritance.

On this basis Levit and Pessikova find that diabetes mellitus may be considered as dependent upon a dominant gene with a penetrance of about 10 per cent.

The recognition of a genetic background for a disease does not in the least imply that it cannot be cured or alleviated. It does bring to the foreground, however, the possibility of early diagnosis in relatives of the patient, with the consequent opportunity of instituting preventive therapy in those relatives who show preclinical or laboratory signs of the disease. For example, it has been suggested that the families of diabetic patients be examined with a view to prevention. The pre-diabetic case may be found to have a prolonged rise in blood sugar for some time before the appearance of sugar in the urine, and for a very considerable time before the onset of symptoms. Proper dietary measures begun early, and

the administration of insulin at the very onset of pancreatic damage, may be the means of preventing diabetes from becoming an outspoken disease in that patient.

Diabetes insipidus is a chronic disease characterized by marked thirst and the excretion of large quantities of a pale urine of low specific gravity. There are two types: secondary or symptomatic, associated with pathologic anatomic lesions at the base of the brain in the pituitary or mid-brain region; and primary or idiopathic, which is the hereditary type. The etiology of the hereditary type is unknown, but is probably a hereditary defect in the pituitary mid-brain system. It appears to be due to a dominant factor with somewhat reduced penetrance.

Renal glycosuria must be carefully differentiated from true diabetes. There is sugar in the urine but no rise of blood sugar, and the condition is a relatively harmless, nonprogressive anomaly. It is inherited as a dominant. Macklin records a practical application of the knowledge of the heredity of this condition. A man applied for life insurance, but was turned down because of sugar in the urine. The family physician, hearing of it, used his knowledge of heredity, knowing that the man's mother suffered from orthoglycemic glycosuria, and demonstrated that the patient was not a diabetic and that his condition would not be expected to shorten his life. The man was accepted.

Endemic goitre is an enlargement of the thyroid gland in response to the demands of an iodine-starved body. Not everyone in a region where goitre is endemic gets goitre. The threshold for iodine intake varies for different individuals. This variation in efficiency of the thyroid, especially where the iodine intake is small, is

hereditary. Goitre is four or five times as common in females as in males. Identical twins show a greatly increased concordance over fraternal twins in the incidence of goitre.

Davenport postulates the interaction of two genes, one a dominant sex-linked gene probably involving a hormone, and the other a dominant autosomal gene, responsible for some imperfection in the structure or chemical action of the thyroid gland itself. The two genes occurring together in an individual result in susceptibility to goitre which will be manifest even under slight iodine deficiency.

Kemp suggests a single sex-linked dominant factor with nondisjunction (a chromosomal aberration). If one supposes that the threshold in women is lower than that in men because of hormonal reactions, a single autosomal dominant gene with slightly reduced penetrance might explain the results.

At present, on account of variable iodine intake and other environmental influences, plus a rather involved genetic picture, the genetic background of goitre must be considered of rather limited practical application. However, the more the environment is controlled, the more important will the hereditary influence become in the remaining cases of goitre; and the future, with its inevitable development of more exact knowledge, may very well see practical applications appear.

In addition to simple enlargement of the thyroid gland due to lack of iodine, diseases of the thyroid include hypothyroidism and hyperthyroidism. Hypothyroidism involves insufficiency of the gland, with absence or

fibrous atrophy, and decrease or absence of its secretion. The hypothyroid conditions include the following.

Cretinism (Curling 1850). This condition, which originates during foetal life or early infancy, involves the complete or almost complete lack of thyroid secretion. Mental and physical development are both retarded. The genetic factor involved apparently predisposes the embryo to failure of thyroid development under a reduced iodine content of the mother's body. Usually one or the other parent of a cretin suffers from goitre or some mild form of thyroid disease, but cretinism is evidently the result of the interaction of environmental factors involving low iodine intake and a genetic factor of some sort involving predisposition towards a severe response to the low iodine.

Myxodema (Gull 1873) is the adult form of cretinism and does not give evidence of any genetic basis.

In addition to hypothyroid conditions, hyperthyroidism occurs, involving a hyperactive state of the thyroid gland, with excessive, probably abnormal, secretion. Treatment is surgical. The types of hyperthyroidism are as follows.

Exophthalmic goitre (Graves 1835, Basedow 1840). This is a disease involving hyperplasia and hypertrophy of the thyroid gland, frequently with fatigue, pulsation, exophthalmos, and tachycardia. It occurs most frequently among young adults, especially women. Focal infection or nervous shock may precipitate the condition, but it appears to occur in those who are constitutionally susceptible. Levit and others have presented good evidence that the constitutional susceptibility depends upon a recessive gene.

Toxic adenoma with hyperthyroidism may be a clinical variation of exophthalmic goitre, as DuBois and others believe, or it may be an independent form of hyperfunction of the thyroid. It occurs usually during the fourth decade, and exophthalmos and tremor are lacking.

Hypertension. A permanent increase in blood pressure may be associated with various things, such as hypertrophy of the left ventricle, renal disease, diet, arteriosclerosis, endocrine disturbances, and others; but in many instances hypertension seems to be a clear case of hereditary predisposition.

Weitz and others find that practically all hereditary cases are accounted for by the presence of a dominant gene. Identical twins usually show the same degree of hypertension. In one case identical twin girls, one doing hard physical toil in factories and on farms, the other living in well-to-do circumstances in town, had essential hypertension at the same time.

As a practical application, advice may be given to the children in hypertensive families. At least by the age of 30 such individuals should have semiannual urinalyses and blood pressure determinations. If the signs are positive, the patient should change the tempo of his life, cut down weight if overweight, limit his activity, and indulge in no strenuous sports, temperamental upsets, and nervous strains.

Allergies. An allergy is a natural hypersensitiveness of an individual to an antigen, as contrasted with anaphylaxis, which is artificially induced. The allergies include asthma, angioneurotic edema, edema of the glottis, eczema, hay fever, urticaria, etc. Possibly migraine should be included. Nearly everyone at some

time or other shows evidence of minor allergy, but major allergy, or true atopy, occurs in only a small percentage of the population. It is true atopy which gives evidence of a genetic basis.

Practically all physicians who have investigated atopy from a genetic standpoint agree that it is due to a dominant gene, with variable expressivity, meaning in this case that it is not specific. A recent study from the Balyeat Hay Fever and Asthma Clinic indicates that the allergic tendency itself is due to a dominant gene, but that the various kinds of allergies are induced by specific modifying genes. These modifiers may be brought in by a normal parent who lacks the main gene. Other investigators, while agreeing on the dominance of the allergy gene, consider the specific type of allergy to be induced by the exigencies of early environmental contact with an allergen.

Wiener, Zieve, and Fries present good evidence that the homozygous condition of the gene for allergy results in allergy before puberty, while the heterozygous condition brings about the allergy after puberty, if at all. The penetrance is reduced in the heterozygous condition.

Migraine appears to be more specific than the other allergies, if indeed it can be considered an allergy at all. Migraine appears to be dependent upon a specific dominant factor, with high penetrance and good expressivity.

Enuresis. Frary studied enuretic families including 787 individuals, 239 of whom had enuresis. The conclusion was reached that enuresis is due to a recessive gene. No cases were included where enuresis could be attributed to a congenital anomaly, a mental defect, a known endocrine disturbance, or associated pyuria (pus

in urine) or nephritis. Children under 3 years were excluded, since the age of 3 years was set as an arbitrary limit for the control of the bladder. The proportion of cases in which the genetic factor is operating has been placed at one third.

Normally the control of the bladder is brought about by environmental conditions. In mild enuresis environment plays a most important part. In the severe cases, however, enuresis runs its course regardless of training. The primary application of these findings is in the psychological approach. "The intelligent mother will accept the challenge of a handicap which may be controlled with a degree of openmindedness and patience which she would not assume in dealing with 'carelessness' or 'naughtiness.' The child himself receives a new impetus to control the enuresis when he is made to understand that it is not entirely his fault, and that he must try hard if he is to have a dry bed" (Frary).

There is no specific cure for enuresis. Frary recommends restriction of the total fluid intake.

Susceptibility to Infectious Disease

A familiar observation is that for certain diseases anyone seems susceptible, while for others only certain people are so. In families, some diseases run through the whole family when one gets it, while in other diseases, some get it and some do not. In such cases, it is worth while to examine the possible hereditary background.

Scarlet fever is one of the diseases to which everyone is not similarly susceptible. In families when one child gets the disease, some children will have it and others do not get it at all. Of course, here the possible relation of

metabolic condition at the time of exposure must be considered. Ratios seem to indicate the possibility of a simple recessive hereditary influence on susceptibility.

Measles. While susceptibility varies, and may be inherited, a more striking fact is that certain families occur in which the members are unable to acquire an immunity, and have repeated attacks, as contrasted with the usual condition of one attack producing immunity.

Diphtheria. Hirszfeld, Hirszfeld, and Brokman state that susceptibility is recessive. When both parents are susceptible, all the children are susceptible.

Tuberculosis is primarily caused, of course, by infection with the tubercle bacillus. Other environmental agencies aid in development of the disease (poor nutrition, occupational conditions, such as inhalation of dusts, etc.). But nearly everyone is infected with the tubercle bacillus, and yet only a fraction of the population dies of tuberculosis. As in cancer, tuberculosis tends to attack the same organ, or even the same part, such as the right or the left lung, in families. Likewise it tends to occur at the same age in the members of a family. Again identical twins show evidence of being strikingly alike in their development of tuberculosis as contrasted with less concordance in fraternal twins.

The hereditary factors are not understood, but in general the susceptibility to tuberculosis appears to be recessive. Thus if both parents suffer from tuberculosis, or if one parent does and the other has tuberculous relatives, the children should be carefully watched for the development of the disease.

Differences in races as to susceptibility also provide evidence for inheritance. Negroes are markedly less sus-

ceptible to malaria and yellow fever than whites, but more susceptible to tuberculosis. This is due to selection, since there is no tuberculosis in the homeland of the Negroes. So also natives of Hindustan are less susceptible to cholera and more to tuberculosis. There is no tuberculosis native to Hindustan.

The comparison of concordance and discordance in identical and fraternal twins has frequently been used as a source of information concerning the genetic nature of a disease or anomaly. If the concordance is significantly higher in identical twins than in fraternal twins, evidence for the genetic nature of the condition has been postulated. It might logically be asked whether it is ever found that fraternal twins show equal concordance with identical twins. It has been shown by von Verschuer that if one twin develops *lobar pneumonia*, the other twin develops it in a certain proportion of the cases regardless of whether he is an identical twin or a fraternal twin. Hence we may say that differences in genetic constitution have little or no influence on the development of pneumonia.

8

Diseases of the Blood

In the study of pathologies of the blood, as in the study of all human characters, progress is made more rapidly when it is recalled that hereditary and environmental influences are both at work in the production of any particular condition. When variations from the accepted normal are obviously due largely to changes in the environment, we are accustomed to speak of the variations as "nonhereditary." When on the other hand, variations in a character can be shown to be due to differences in genetic constitution, we speak of the variations as "hereditary." It is essential to bear in mind, however, that the resultant character in either case is the end-product of specific hereditary factors developing in a particular environment.

With these thoughts in mind we are not doing violence to medical assumptions in considering always the possibility that variations in the blood picture and the clinical symptoms which are frequently correlated with such variations may be dependent on inherited variations in the genetic make-up of the individual. Certain of these clinical manifestations are very definitely correlated with specific types of hereditary behavior.

The Hemorrhagic Diatheses

Foremost among these is *hemophilia* (Otto 1803, Nasse 1820), involving a plasma which will not permit the

disintegration of the platelets. Here the condition is clearly the result of a specific recessive sex-linked factor.

Birch has reported the use of the female sex hormone in the control of hemophilia. While we cannot question the results of this treatment as recorded, its use is based on a fundamental misconception, to which attention should be directed. The author says: "Taking into consideration that only males have the disease, while it is transmitted through the unaffected female, one is forced to the conclusion that if the female can transmit the disease, she must potentially have the disease. Then there must be something in the female mechanism which holds the disease in abeyance." Based on this assumption, ovarian extract and ovarian transplants were used as a means of control for hemophilia with apparently good results.

It must first be pointed out that it is not in the least necessary to assume that because unaffected females can transmit the disease they must potentially have the disease. Such a conclusion is contrary to all genetic principles. Hemophilia is known to be a sex-linked character. Males show it with a definite frequency because only one of the pair of sex chromosomes in the male carries the factor, thus making a single dose of the factor *h* for hemophilia effective. In women, a single dose of the factor will be recessive to the normal dominant allele on the other member of this pair of chromosomes. Unaffected males also have this normal dominant factor *H*. Of the women who transmit the disease, practically all, if not absolutely all, will be heterozygous, free from the symptoms because of the presence of the normal dominant allele.

There is thus no a priori reason for supposing that the female sex hormone should be a specific for the control of hemophilia. It is known that injection of a foreign protein is efficacious as a control for this disease (Minot and Buckman 1927), and it would seem safer to assume that the results recorded by Birch are manifestations of a more general phenomenon than to invoke a more specialized and definitely questionable hypothesis as an explanation.

The possibility exists that females receiving the double dose of the gene for hemophilia may live without manifesting symptoms of the disease. This is unlikely from a genetic standpoint, but if it were the case, Birch's hypothesis might still be tenable. This brings up again the old question as to the fate of homozygous hemophilic females. Do they exist with the symptoms of the disease? Do they exist as apparently normal individuals because of some protective mechanism? Has such a zygote ever been formed and the result recorded? Or is a double dose of the gene lethal, so that they never exist at all? Geneticists have favored the last hypothesis.

A female of the formula *hh* would only be expected to occur when a hemophilic man married a woman who was a carrier, or who was herself hemophilic. How often have matings of this sort actually occurred in the pedigrees which have been recorded? In looking for such matings, it is necessary to search for instances where a hemophilic man has a hemophilic son or a hemophilic father-in-law. In such cases he might theoretically have a hemophilic daughter, since the wife would certainly be a carrier. A hemophilic brother or grandfather of the wife, even

though her father were normal, would indicate that she might be a carrier.

Upon examination of 250 published pedigrees of hemophilia, the conditions under which a hemophilic woman would be expected to arise are found to be extremely rare. This is to be expected, since only 11 per cent of hemophilic males live to be 22, and the chances of these marrying carrier females are extremely small. Only one case was found where a hemophilic male had married a carrier woman (Hauser-Veller family, from Stahel 1880). One hemophilic son and one normal daughter were produced.

Among our records at the medical genetics laboratory of the Ohio State University are several cases worthy of note. First is a case where a hemophilic male married a carrier female, as evidenced by a hemophilic son (figure 18). This is apparently only the second authentic case to be recorded. The diagnosis in this family was supported by complete laboratory examination. In the second generation of this pedigree one half of the daughters might be expected to have hemophilia. The two daughters occurring were normal, however, although both were carriers. Here again is no definite evidence for or against the possibility of the realization of a hemophilic female.

The man referred to by the arrow in figure 18 had, as may be seen, three daughters. At the time he was in the hospital and learned of his hereditary condition, these daughters were babies. The man's dying request was that his three daughters should never be told of this hereditary affliction, since he was ashamed of it. This unfortunate attitude is all too common. In this case the daughters are definitely carriers of hemophilia.

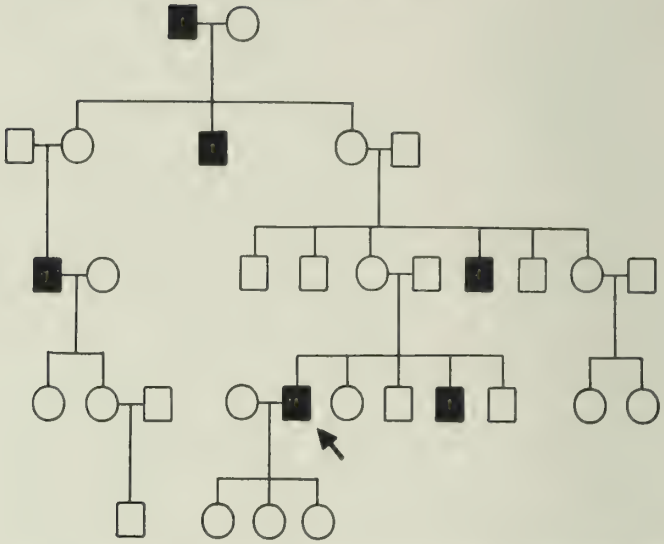

Fig. 18.—A family history of hemophilia in which an affected man married a "carrier."

The unaffected males in hemophilic families cannot transmit the hemophilia, and may safely marry, yet instances are on record where such men were wrongly advised against marriage by uninformed physicians.

Another new pedigree of hemophilia is offered here, chosen from many in our records as showing the practically identical course of heredity through both lines of descent from a known carrier who married twice (figure 19).

Distinguished from hemophilia by differential diagnosis are the *purpuras*, thrombopenic (deficient number) (Werlhof 1735) and thrombasthenic (deficient function of platelets). Relatively few investigations have been made of these conditions from a genetic standpoint, but

such as have been made indicate a hereditary background for the defects, probably dominant factors with reduced penetrance.

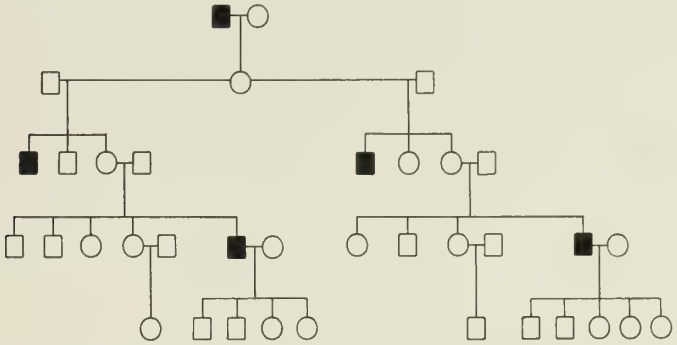

Fig. 19.—A pedigree of hemophilia.

Epistaxis, or severe nosebleed unassociated with telangiectasis, has been recorded in several generations in a family (Babbington 1865, Lane 1916).

Multiple telangiectasia (Rendu 1896, Osler 1901), a dilation and spider-webbing of the capillaries, frequently with hemorrhage, is apparently due to a dominant factor. Many cases showing hereditary transmission are available, in some instances running through five generations.

An example of the value of a knowledge of the hereditary nature of a condition in diagnosis has recently been published by Macklin. A man was admitted to a hospital, having lost considerable blood by hematemasis. The diagnosis would ordinarily have lain between Banti's disease, cirrhosis of the liver with esophageal varices, or gastric ulcer. The man was put under observation. One of the attending physicians, however, knew the man's

father, who had telangiectasia with spider-webbing of the capillaries of the nasal mucous membrane. Knowing the dominant nature of the hereditary telangiectasia, the son was examined, and a large telangiectatic spot was excised. The patient promptly recovered, and there was no recurrence of the hemorrhages over a period of more than five years. Here the knowledge of the hereditary nature of the condition led to correct diagnosis and hence to proper therapy.

Phlebectasis, an abnormal dilation of the veins, has been recorded as the result of a dominant factor.

Hemoptysis, involving profuse bleeding from the lungs, beginning at puberty and continuing at intervals throughout life, has been presented as the result of a dominant factor. No tuberculosis or other apparent cause could be found in these cases. The condition was not fatal and did not seriously impair the health. The coagulation time was not prolonged.

Eosinophilia. There have recently been presented several families in which eosinophilia was transmitted, probably as a dominant factor. The normal range of 2 to 4 per cent was increased to as much as 40 per cent. In these families the known causes of eosinophilia (trichinosis, allergy, dermatoses, etc.) were ruled out (Stewart 1933).

The Anemias

Every anemia results from a loss of balance between the formation and the loss or destruction of red blood cells. The normal method of disposal of worn-out or otherwise injured cells is hemolysis. About a trillion

erythrocytes, comprising 1/25 of all circulating erythrocytes, are said to be disposed of by hemolysis each day. The spleen plays a major role in this removal. The average life of a normal erythrocyte seems to be about 30 days. Normally a delicate balance is maintained between

TABLE 11.—*The Anemias*

(Those having a genetic basis are printed in capital letters.)

I. Due to blood loss (the post-hemorrhagic anemias).
   A. Nonhereditary causes (trauma, surgery, etc.).
   B. Hereditary causes (TELANGIECTASIA, HEMOPHILIA, etc.).

II. Due to increased blood destruction (the hemolytic anemias).
   A. Damaged cells.
      1. Chemical agents (phenylhydrazine, snake venom, etc.).
      2. Bacterial toxins (gas gangrene, etc.).
      3. Immune hemolysins (transfusion reactions).
      4. Parasites (malaria, etc.).
   B. Congenitally abnormal cells.
      1. Abnormal shape.
         a. SPHERICAL (HEMOLYTIC ICTERUS). Dominant.
         b. OVAL (OVALOCYTOSIS). Dominant.
         c. SICKLE (SICKLOCYTOSIS). Dominant.
      2. Abnormal structure.
         a. ERYTHROBLASTIC ANEMIA. Probably recessive.
         b. SICKLOCYTOSIS. Dominant.
   C. Abnormal activity of spleen and other reticulo-endothelial cells.
      1. LEUCEMIA. Dominant but very low penetrance.
      2. HODGKIN'S DISEASE. Slight evidence of heredity.
   D. Unknown cause.
      1. Paroxysmal nocturnal hemoglobinuria.
      2. Various idiopathic hemolytic anemias.
      3. ERYTHROBLASTOSIS. Probably recessive.

III. Due to inadequate blood formation (the aregenerative anemias).
   A. PERNICIOUS ANEMIA. Antecedent achlorhydria probably dominant.
   B. Sprue.
   C. GAUCHER'S DISEASE. Probably recessive (see table 12).

formation and loss or hemolysis of erythrocytes. When this balance is upset, an anemia may result.

The Posthemorrhagic Anemias

Most anemias due to loss of blood will of course be environmental, due to trauma, surgery, hematemasis, hematuria, etc., but secondary anemia may result from the loss of blood due to one of the hereditary hemorrhagic diseases already discussed (hemophilia, telangiectasia, etc.).

The Hemolytic Anemias

The loss of balance between formation and destruction of erythrocytes may result from excessive hemolysis. In such an anemia (hemolytic anemia) there will be an increase in bile pigments of the plasma, paralleling the rate of cell destruction, and an increased number of reticulocytes, indicating that cells are being delivered very rapidly from the bone marrow.

Hemolytic icterus (Minkowski 1900, Chaufford 1907) is the result of a dominant factor, with complete penetrance but variable expressivity. The expression varies from clinical manifestations of jaundice and chronic anemia, to preclinical or laboratory signs, such as reticulocytosis, microspherocytosis, increased fragility in hypotonic solutions of sodium chloride, and enlarged spleen. Lord Dawson in the Hume Lectures indicates that the medical profession is coming to doubt the existence in the strict sense of the word of an acquired hemolytic icterus, believing rather that latent cases are the result of previously low expressivity of the genetic factor.

An excellent example is furnished by a case from the Ohio State University Hospital. Here the patient showed

both clinical symptoms and laboratory signs, while five of the seven sons on examination, although presenting no clinical symptoms, showed one or more of the laboratory signs, including microcytosis, increased fragility, increased number of reticulocytes, and secondary anemia. A practical application of the knowledge of the hereditary condition is apparent here, involving the recurrent examination of these sons looking to the possible need of a splenectomy. (A splenectomy was done on the father with good results.) Prophylactic splenectomy is indicated in preclinical cases, inasmuch as such things as infection or a broken limb may precipitate the crisis.

Another family history is presented in figure 20.

Sickle cell anemia (Herrick 1910) is an inherited defect in the quality of the stroma (the fine network in the

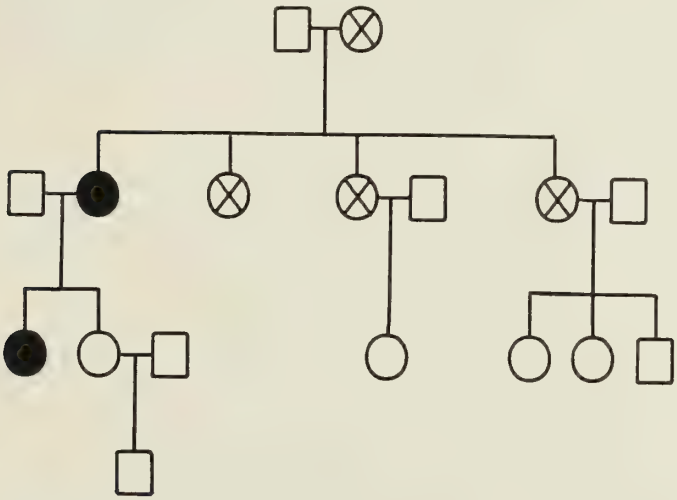

Fig. 20.—A pedigree of hemolytic icterus. The solid symbols indicate persons showing clinical symptoms; the cross-marked symbols indicate persons showing only laboratory signs of the disease.

interior of the cell), resulting in disintegration, and removal of the cells by the spleen. The cells take on a sickle or stellate shape in vitro. The symptoms vary from subclinical to severe clinical anemia. The trait, found almost exclusively in Negroes, is due to a dominant factor.

Oval cell anemia (Dresbach 1902) is a rare condition involving an oval shape of the erythrocytes, not ordinarily resulting in clinical anemia. Unlike sickle cell anemia, there is no racial tendency. The condition is due to a dominant factor.

Erythroblastic anemia or Mediterranean anemia (Cooley and Lee 1925, Cooley 1928) is usually noted in infancy or early childhood, and the majority of cases die before puberty, although the condition has occasionally been reported in adults. It is restricted to the Mediterranean races and their descendants. There is a rather constant anemia, with poor health, lack of appetite, and failure to grow, and with a Mongoloid cast of countenance. It is apparently due to an autosomal recessive factor.

Leucemia (Bennett 1845). Genetically the myelogenous and lymphatic types of leucemia do not seem to be fundamentally different, since both types have been observed within the same family group. Recent studies by Ardashnikov indicate a dominant factor for leucemia, but with an extremely low penetrance, amounting to but a fraction of 1 per cent.

Hodgkin's disease (Hodgkin 1832, Wilkes 1856). There have been one or two suggestions of a genetic basis for Hodgkin's diseases, but the evidence for this is negligible.

Erythroblastosis or icterus gravis neonatorum (Buchan and Comrie 1909, Rautman 1912, Buhrman and Sandford 1930, Blackfan and Baty 1932). A disturbance of the metabolism of the hematopoietic system, frequently involving jaundice in the first few days of life, with a severe anemia and bleeding tendency. There is a high mortality (about 75 per cent). The condition is apparently dependent upon a recessive gene with variable expression including icterus gravis, generalized congenital hydrops with or without jaundice, and severe congenital anemia. When an infant shows one of these conditions with erythroblastosis, another child may well be born into the family showing another manifestation, a possibility of which the parents should be warned. In case another child does develop one of the manifestations, previous arrangements for emergency transfusion may see it through the critical period. Splenectomy and liver therapy have also been suggested.

The Aregenerative Anemias

Pernicious anemia (Addison 1849, Biermer 1868). Macrocytic anemia may be due to the failure of an intrinsic factor or of an extrinsic factor. Achlorhydria, which is genetic (probably dominant), may be followed by destruction of the pyloric glands and hence by a lack of the intrinsic factor. Lack of meat, milk, and eggs in the diet may result in the lack of the extrinsic factor. Hence macrocytic anemia may be in some cases genetic, and in other cases environmental. In the genetic instances, of which pernicious anemia is an example, incipient cases may be sought and diagnosed in the relatives of patients, by looking for the gastric juice

alterations which antedate the actual disease. Proper therapy may thus be instituted before the blood picture in the circulation is altered, perhaps before the hemato-

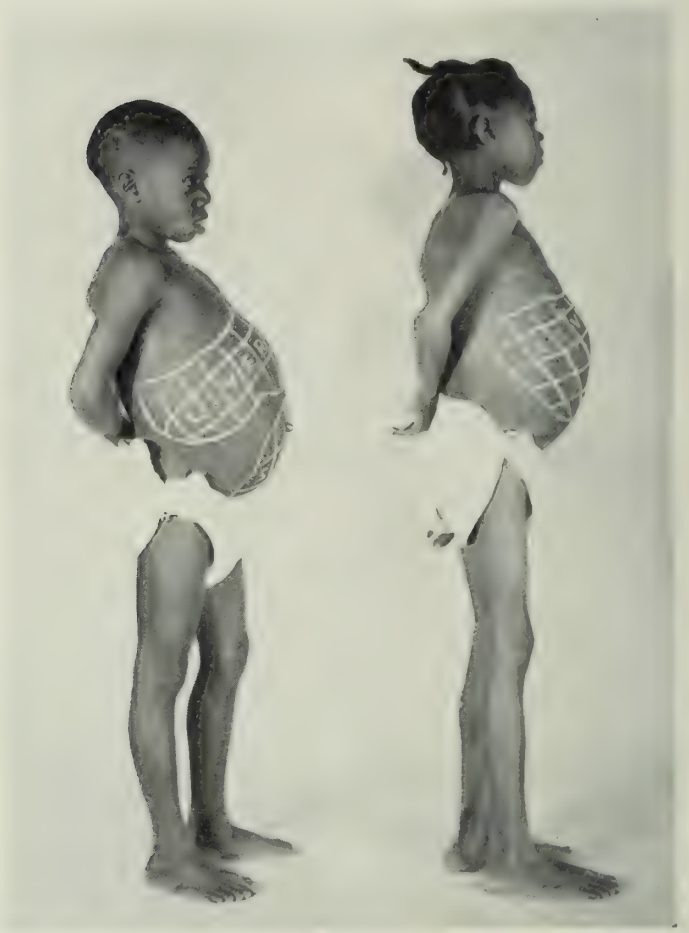

Fig. 21.—A brother and sister with Gaucher's disease.

poietic system undergoes its primary change, and certainly before the nervous symptoms become manifest.

Sprue, and other macrocytic anemias of the tropics, are apparently always due to a deficiency of the extrinsic factor, and are therefore environmental and not genetic in nature.

Gaucher's disease or cerebroside lipoidosis (Gaucher 1882) is one of the storage diseases to be described below, but is included here because of the anemia that may accompany the disorder (see tables 11 and 12). The complex lipoid kerasin is deposited in the hyperplastic reticular cells of the hematopoietic system. It is apparently dependent upon a recessive factor (figure 21).

Storage Diseases

Along with Gaucher's disease may be discussed the xanthomatoses and other storage diseases (see table 12) which do not ordinarily result in an anemia.

TABLE 12.—*The Storage Diseases*

(Those known to have a genetic basis are printed in capital letters.)

I. Storage of internal products.

A. Proteins.

1. Amyloidosis. Amyloid substances stored in vascular connective tissue.
2. Scleroderma. Collagen stored in skin and subcutaneous connective tissue.

B. Carbohydrates.

1. GLYCOGEN DISEASE. Glycogen stored in liver, kidneys, heart and muscles. Recessive.
2. DIABETES MELLITUS. Reducing sugars stored in blood serum and various organs. Dominant, with only 10 per cent penetrance. (See chapter 7.)

C. Lipoids.

1. Obesity. Neutral fat stored in fat cells. Some forms of obesity may have a secondary genetic basis.
2. Lipomatosis. Neutral fat stored in fat cells and hepatic cells.

3. GAUCHER'S DISEASE. Kerasin stored in reticulo-endothelial cells, epithelial and connective tissue cells. Recessive.
4. NIEMANN PICK'S DISEASE. Phosphatides stored in reticulo endothelial and other cells. Recessive.
5. HAND-SCHÜLLER CHRISTIAN'S DISEASE. Cholesterol esters stored in reticulo-endothelial cells. Recessive.
6. TAY-SACHS' DISEASE. Phosphatides stored in reticulo endothelial cells, glia and ganglion cells. Recessive.
7. GARGOYLISM. Lipid stored in brain and other tissues. Recessive.
8. Lipoid nephrosis. Cholesterol ester stored in reticulo-endothelial cells, renal epithelium and blood.

D. Decomposition products.
1. GOUT. Urate stored in connective tissue cells and cartilage. May be dominant with very low penetrance.

E. Minerals.
1. Calcinosis. Calcium stored in connective tissue, interstitial and epithelial cells.

F. Pigments.
1. JAUNDICE. Bilirubin stored in all organs. Several types of jaundice have a genetic basis. See under anemias.
2. Addison's disease. Storage of melanin in skin and mucous membranes.
3. Pigment atrophy. Storage of lipofuscin in heart, liver and ganglion cells.
4. PORPHYRIA. Porphyrin stored in bones and other organs. Recessive.
5. Hematochromatosis. Hemosiderin and lipofuscin stored in skin, liver, pancreas and kidneys. Slight evidence for heredity.
6. OCHRONOSIS. Melanin-like dyes stored in cartilage and ligaments. Alkaptonuric cases are due to a recessive factor.
7. Malaria. Malaria pigment stored in reticulo-endothelial cells.

G. Water.
1. Edema. Water stored in parenchymatous cells and interstitial substances.
2. CONGENITAL HYDROPS. See erythroblastosis under anemias. Recessive.
3. TROPHOEDEMA. Edema of the legs. See under skin diseases. Dominant.

II. Storage of external products.
   A. Industrial. Storage in the reticulo-endothelial tissues of silicates, dyes, rust, chemicals, vapors, etc.
   B. Medicinal. Storage of arsenic, copper, iron, lead, silver, etc.

Niemann-Pick's disease or acute idiopathic xanthomatosis (Niemann 1914, Pick 1922) appears to be due to a recessive factor. The stored lipoids are in this case phosphatides, and the disease is fatal within the first two years of life.

Hand-Schüller-Christian's disease or chronic idiopathic xanthomatosis (Hand 1891, Schüller 1916, Christian 1919) involves the storage of cholesterol-fatty acid esters. The course of the disease is slow, but death usually results by the third decade. The inheritance is not certain, but is most probably recessive.

Tay-Sachs' disease or juvenile amaurotic idiocy (Tay 1881, Sachs 1887) is in some way related to the xanthomatoses, and may be combined with Niemann-Pick's disease in some cases. Phosphatides are stored in the reticulo-endothelial cells, glia and ganglion cells. This condition has already been discussed as a recessive lethal trait in chapter 3, where it was included because of the mental symptoms.

Gargoylism or lipochondrodystrophy (Hunter 1917, Hurler 1919) involves the deposition of a lipoid substance in the brain and other tissues. It is characterized by a large head, short trunk, protruding rounded belly, and flexed fingers. Early death is the rule, commonly from heart failure. This condition combines some of the features of Niemann-Pick's disease and Morquio's disease (chapter 6), but appears to be a clinical entity dependent upon a recessive factor

Glycogen disease (von Gierke 1929) involves the excessive accumulation of glycogen in the liver and other organs. The liver and kidneys may be greatly enlarged, but there is no splenomegaly. The disease is not fatal, and appears to depend upon a recessive gene.

Ochronosis with alkaptonuria (Virchow 1866, Albrecht 1902). Ochronosis is a rare metabolic disorder in which the skin is pigmented, the cartilages and fibrous tissues are blackened, and the urine is dark because of the presence either of alkapton (homogentisic acid), melanins, or carbolic acid derivatives. All cases of ochronosis do not exhibit alkaptonuria. In those cases which do show alkaptonuria, a recessive factor seems to be responsible. The condition is relatively harmless.

Porphyria (porphyrinuria) may be congenital or acute. The congenital form appears to be recessive, and is benign. Porphyrin is stored in the bones and other organs, and excreted in the urine. Repeated eruption of skin blisters occurs, and the fingernails may be lost. Porphyrinuria may be the result of malaria, pellagra, lead poisoning, cirrhosis, tonsillitis, and other conditions; these forms are of course not genetic.

Hemochromatosis (Hanot and Chaufford 1882) involves the deposition of iron-containing pigments (hemosiderin and hemofuscin) throughout the body. There is a suggestion of a recessive hereditary basis, but no clear proof of it as yet.

In the recessive conditions just described, many of which are lethal, it is important to remember that when one child has the condition, there is a very real danger of its repeating itself in subsequent offspring of the same parents.

Other storage diseases, such as diabetes mellitus and trophoedema, are discussed in more appropriate places, as any classification of diseases must have a certain amount of overlapping. Consult the index for hereditary storage diseases listed in table 12 but not discussed in this chapter.

9

Cancer

The subject of cancer always arouses great interest, and this interest has been reflected in the work of the medical geneticist. Cancer is a trait, however, for which genetic data are not easily obtained and for which clear-cut results and conclusions are not readily arrived at for the following reasons.

Cancer does not ordinarily appear until later in life, so that we cannot use the usual families of parents and children for the source of data. The diagnosis of malignancy is not always correctly made. Many persons who have cancer, and even many who die of it, are not listed as having this disease. Family records for cancer are not carefully kept. Few people know what caused the death of their grandparents or whether they ever had tumors. Many individuals die before the cancer age. We cannot be sure whether or not they would have developed the disease. Cancer is of various kinds, which may be the result of different genetic factors or various environmental stimuli. Controlled experiments along these lines are difficult to make in human beings.

In spite of these difficulties there is at hand a considerable body of data bearing on the possibility of a genetic basis for the tendency to produce tumors.

Tumor formation is the result of the stimulation of tissues to growth. The stimuli may be inherent in the

individual, or they may be extrinsic, such as trauma or irritation, but all individuals do not react alike to them. Roentgen ray workers differ in their responses to the same amount of exposure. Paraffin workers show a much higher proportion of skin cancer, especially of scrotum and thigh, than the control population, yet the incidence in paraffin workers is less than one per cent.

Cancer occurs in about 10 per cent of all those past forty. Hence on the basis of chance alone we should find some families with a high incidence of cancer. Chance alone, however, does not explain the frequency with which the same type of cancer affects the same organ at the same age in various members of a family. The studies of Warthin, Wells, Macklin, Martynova, and others have brought together a host of material bearing on the genetics of cancer in man.

Identical twins furnish some interesting evidence. Champlin (1930) reports a case of identical twin boys, one of whom was struck in the right testis with a board. He developed sarcoma of the right testis at 24, and died at 26 as a result of delay in treatment. The other twin, in the absence of trauma, developed a similar sarcoma of the right testis at 31, and was cured by early removal of the testis. Several possibilities suggest themselves by this and like cases. First, it appears that cancer due ostensibly to trauma might very well appear, although at a later date in the absence of trauma; in other words, the trauma merely hastens the expression of an innate tendency for uncontrolled growth.

Second, there exists a brilliant opportunity for the physician to diagnose early, and thus in many cases to cure, cancer in relatives of cancer patients. In the case

of an identical twin this opportunity should never be overlooked.

Other cases of similar cancers in the two members of a pair of identical twins are on record: retinal blastoma of the left eye (Benedict), cerebellar tumors (Leavitt), adenosarcomas of the uterus (Croom), ovarian cysts on the same side (Twinem), glioma of the cerebrum (Joughin), malignant teratomas of the ovary (Warthin), fibro-adenoma of the same quadrant of the left breast at the early age of 21 in each case (Burkard), and many others.

There is a strong impression in spite of data like the above that trauma is the prime cause of cancer. Warthin took especial delight in presenting family histories which controverted such an assumption. Among these was a family in which for three generations the father had been a smoker, and had developed cancer of the lip. In the fourth generation, under Warthin's observation, three sons who were smokers developed cancer of the lip between the ages of 40 and 45. The fourth son, who was a nonsmoker, developed cancer of the lip at 63.

In another revealing family among the many collected by Warthin, cancer of the lip had again appeared in the father of the family, who was a smoker, for each of three generations. In the fourth generation, which Warthin observed, seven sons who were smokers had not developed cancer of the lip, although they were all beyond 65 years of age; the eighth son, a nonsmoker, developed cancer of the lip like that of the preceding generations at 63.

Other facts which seem to indicate the intrinsic, hereditary influence in the production of cancer are, as has been forcibly presented by Macklin, as follows:

Tumors tend to occur at approximately the same age within a family. For example, tumors of the breast are rare before the age of 30, yet Tourneaux reports a family in which the mother had both breasts removed for fibro-adenoma at 14. Her two daughters had both breasts removed for fibro-adenoma at 14 and 16, respectively.

In another family, a mother and two daughters had cancer of the breast at 76, 74, and 70, respectively. Again, a mother died of breast cancer at 21, but by this time she already had three daughters, who later died of breast cancer at 14, 19, and 22, respectively. A mother and her son had polyposis of the rectum at the ages of 10 and 11, respectively. A mother and father both died of gastric ulcer at 60. Six children developed cancer of the stomach at 54, 56, 60, 61, 62, and 63, respectively. In another family the mother died of gastric cancer at 72. Five of the six children died of gastric cancer at ages between 68 and 74.

These and many similar instances indicate a tendency for tumors to occur at the same general age within families. In addition, tumors tend to affect the same organ in various members of a family, and the tumor tends to be of the same type. This is especially striking in cases of rare tumors. For example, a father and five of his children had sarcoma of the neck. A mother and two sons had lympho-sarcoma of the left side of the neck.

Two sisters, three brothers, and the son of one of the brothers all had tumors of the acoustic nerve. A father and two sons had cancer of the throat, and a father and a daughter each developed lympho-sarcoma of the chest and abdomen.

Angiomatosis is a rare tumor of the brain. The few

cases on record are grouped in families. In one such family a father, three children, and two grandchildren each had angiomatosis. In another, a father, son, and daughter, and in still another a father, his sister, and his child, had the condition.

Tuberose sclerosis, or epiloia, involves tumor production. It was discussed as a specific inherited condition under the mental traits.

Retinal glioma presents a striking picture of occurrence within families. A few of the cases are listed here to emphasize the genetic basis. It occurred in 3 out of 12 children in one family (Zabugin), in 3 out of 5 children (Boyd), in 5 out of 14 (Thompson), in 3 out of 5 (McGregor), in 4 out of 7 (Lerche), in all 4 (Sickel), in all 3 (Moher), in a father and 2 out of 7 children (Degourea), in a mother and 2 sons (Hoffman), in a father and 3 out of 12 children (Purtscher), in a father and 3 children (Sym), in a father and 3 sons (Letchworth), in a mother, her daughter, and 4 grandchildren (Griffith), in a child and 2 uncles and an aunt (Feinstein) and many others.

Martynova has recently demonstrated that cancer of the breast is more frequent in all female relatives of such patients than in the general population. It is eighteen times as frequent in the mothers of patients as in the mothers of the control population.

Primary carcinoma of the liver is rare, but two cases are reported each with two brothers involved. Seven cases of sarcoma of the choroid in one family were reported by Davenport. Gastric cancer is relatively common, and we should expect it within families merely by chance, but there are hundreds of such cases in the literature.

Likewise, since each family involves two parents, frequently with dissimilar ancestries, we must expect to find dissimilar types of tumors within families, but the similarities of tumor type and organ involvement are striking indeed.

Various hypotheses of the type of inheritance to cancer susceptibility have been offered. These run the gamut of dominant, recessive, multiple factors, and modifying factors. Warthin postulates a recessive factor for general cancer susceptibility plus specific modifying factors for organ susceptibility. Trauma or irritation may bring out the effect in susceptible persons earlier than hereditary factors, but intrinsic factors alone are probably sufficient if given time.

If we turn to animals to discover what information they can give us along this line, we find first that pathologists are agreed that tumors in all mammals represent essentially the same conditions, varying only in the frequency of involvement of different tissues in various species. For example, thyroid tumors in mice, dogs, and men show the same peculiarity of appearing as mixtures of sarcoma and carcinoma. Basal cell carcinoma both in mice and in men appears chiefly on the faces of old individuals and does not produce metastases. Histologically the various tumors in animals and men are similar.

Second, there is no question as to the hereditary significance of cancer susceptibility in animals. In horses, dogs, cattle, mice, and others, spontaneous tumors occur in some lines and not in others. In the domestic cow, where the mammary gland is subjected to so much overstimulation, abuse and trauma, no cancer develops, as has been pointed out by Wells. Only two cases have ever

been described, yet the mammary gland is one of the commonest sites for cancer in mammals generally.

Comparative pathology presents other evidence. Species tend to be specific in the type of cancer they develop. In swine a mixed tumor of the kidney is common; in sheep primary epithelial tumors of the liver regularly occur.

Although transplantable tumors have contributed much to the knowledge of the genetics of cancer in animals, it is the study of spontaneous tumors which throws most light on human cancer. In mice the genetic constitution has clearly been shown to play an important role in determining not only whether an animals will develop cancer, but what kind of cancer it will develop, and in what organ. Even in experimental animals, however, the exact mode of inheritance is not very clear. Slye considers it a simple recessive. Little and others do not think it as simple as this. For mammary cancer, Little postulates extra-chromosomal, cytoplasmic factors in addition to chromosomal genes.

While there are undoubted genetic differences in regard to the tendency to produce cancer in many animals, there are certain exceptions. For example, Dunning, Curtis, and Bullock are convinced that the potency for malignancy in rats must be a universal cell characteristic, and the histogenesis of chemically induced tumors as well as those induced by Taenia larvae is determined by fortuitous exposure to irritation of the various types of cells. Rats, then, in contrast to mice, do not seem to differ genetically in regard to factors for the response to irritation. This is simply another manifestation of species differences in genetic behavior.

Summing up the evidence for the inheritance of a tendency for the production of tumors in man, we find:

1. Identical twins have the same type of cancer in the same organ at approximately the same age.
2. Cancer which is seemingly due to trauma or irritation in one twin or in some members of a family will frequently appear later on in the other twin or in other members of the family in the absence of trauma or irritation.
3. Tumors tend to occur at approximately the same age in the various members of a family.
4. Tumors tend to affect the same organ in the various members of a family.
5. The same type of tumor tends to affect the various members of a family.
6. Experimental animals provide supplementary evidence that the tendency to produce tumors as well as the lack of such tendency may be inherited, both by the standard chromosomal mechanism and by cytoplasmic factors. Such experiments likewise bring to the fore the part played by carcinogenic agents in causing or hastening the production of tumors in genetically susceptible individuals or species.

In putting the knowledge of the genetic basis for cancer into use, the following points may be borne in mind. Periodic examinations of the various members of a "cancer family" may offer the opportunity for early diagnosis and prevention. In the case of rectal cancer, for example, rectal carcinoma frequently develops upon the basis of polypous masses, which persist for some time

before cancerous change sets in. Early removal of these may prevent the development of the cancer.

Warthin states that the individual with a strong history of cancer in the family should take heed. He should avoid all the known extrinsic agents associated with the etiology of cancer. Chronic irritation should be removed or obviated. He should not engage in any industry in which mineral oil, tar, paraffin, or other irritating products are used. He should not expose himself to irradiation. Rough pigmented moles should be removed. Scars of the skin should be treated by skin grafting. Chronic inflammatory conditions should be healed as quickly as possible. Finally, he should not marry into another family with a strong history of cancer.

10

The Future Development of Medical Genetics

One of the ideals of medical genetics is to have available maps of the human chromosomes, in which the position of each gene will be known with reference to each other gene. Such maps could be of great importance in genetic prognosis.

Since genes are carried on chromosomes, and since there are so many pairs of genes and so few pairs of chromosomes, it is clear that many pairs of genes must be carried on each pair of chromosomes. The pairs of genes carried on one pair of chromosomes are said to be *linked*. As a result of linkage, wherever one gene on a chromosome goes in hereditary transmission, the other genes on that chromosome must go too, with certain exceptions. The exceptions are those cases in which the two members of a pair of chromosomes exchange homologous parts (and thus blocks of genes) during the reduction division. The occasional exchange is known as *crossing-over*.

Because of linkage certain genes, and thus the traits they control, will tend to be inherited together. By testing this tendency the strength of the linkage may be determined. The strength will vary between various genes. In general, the closer two genes are on the chromosome, the more they tend to remain together in transmission.

In experimental animals and plants the linkage of various factors has been carefully tested, and maps are available for many species showing the genes on each chromosome arranged in their proper linear order. Of course either allele of a pair of genes may be present on a given chromosome at a given time. Thus if the pair of factors *A* and *a* are located on a certain pair of chromosomes, and the factors *B* and *b* are also located on that pair of chromosomes, any given chromosome of the pair might have on it at a given time factors *A* and *B*, or factors *A* and *b*, or *a* and *B*, or *a* and *b*.

If one member of the pair of chromosomes carried *A* and *B*, and the other carried *a* and *b*, the genes *A* and *B* would tend to go together to the same germ cells, and *a* and *b* would tend to go together to other germ cells. Crossing-over would reverse these relationships, sending *A* and *b* to certain germ cells and *a* and *B* to others, but the closer the genes were together, the more rarely would the original relationship be disturbed. The per cent of crossing-over can be determined for any linked pairs of genes, so that it can be stated, for example, that *A* and *B* will cross over in only 3 per cent of all cases. In the other 97 per cent they will be transmitted together.

Until recently it has been difficult to study linkage in man, for reasons which need not be gone into here. We now have, however, special mathematical methods of analyzing human family histories for linkage, due to the work of Bernstein, Wiener, Hogben, Fisher, Penrose, and others. A large series of human genes has been tested for linkage by various workers (Burks, Penrose, Hogben, Snyder, et al.) with thus far very few significant cases of linked genes.

The importance of linkage to medical genetics lies in the possibility of locating close to each gene for an important medical character some harmless gene, the effects of which could be recognized in early childhood. By the study of a family in which an important medical condition occurred, it would be possible to predict, when a child was born, just what the chances were that that particular child would develop the condition. If, for example, the blood group genes should be found to be located on the same pair of chromosomes as the genes for Huntington's chorea and its absence, with 5 per cent crossing-over, it would be possible to say in certain cases, "This child has a 5 per cent chance of developing Huntington's chorea," or, "This child has a 95 per cent chance of developing Huntington's chorea."

Such information would be of value in two ways. First, it would give the psychiatrist the opportunity of observing preclinically an individual who would almost surely develop chorea later on. This might lead to the development of preventive measures. Second, it would give more specific information than is now available on the desirability of marriage for the members of such a family who might later develop the condition.

In addition to the blood group genes, the presence of which can be determined in early life, other common and easily recognizable genes are being studied for their possible linkage to genes for important medical conditions. These include the genes for the MN reaction, for taste deficiencies to a number of chemicals such as phenyl-thiocarbamide, for the direction of the occipital hair whorl, and others.

It will be realized that all the genes for sex-linked

characters must be linked together, since they all occur on the X-chromosome. While this must be so, it is very difficult to prove experimentally, since the recessive genes producing the traits are usually very rare. It is difficult to find, for example, a family in which both hemophilia and color blindness occur, or in which there exist both optic atrophy and pseudohypertrophic muscular dystrophy.

The greatest advance in the study of linkage and the mapping of human chromosomes has been made in connection with a new type of human heredity: incomplete sex-linkage. To offer a glimpse into the future of the development of medical genetics, let us examine the study of the sex chromosomes in some detail.

It has been known for a number of years that in certain fishes some sex-chromosome genes are restricted to the X-chromosome, others to the Y-chromosome, while still others are found in both chromosomes, with consequent crossing-over. There are thus three kinds of hereditary behavior associated with the sex chromosomes. Genes found only on the X-chromosome are "sex-linked," and behave in the manner which has become familiar to us in preceding chapters. Genes found only on the Y-chromosome would produce their traits only in males, and these traits would be handed from an affected father to all his sons. Genes found on both the X- and Y-chromosomes would be "incompletely sex-linked," and their peculiar behavior will be discussed below.

It has recently been shown by Koller and Darlington (1934) that the sex chromosomes of mammals have two distinct histological portions: a portion in each which is homologous to the corresponding portion in the other,

and shows chiasmata in meiosis, and a portion in each which is nonhomologous and nonpairing (figure 22).

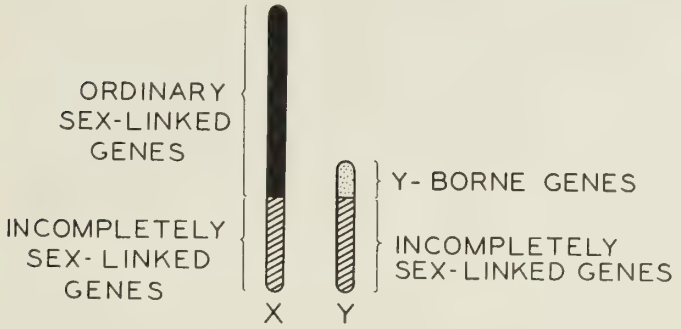

Fig. 22.—Diagram of the sex chromosomes, showing the location of the three types of sex-linked genes.

With this histological observation and with the knowledge of the three kinds of hereditary behavior in fishes, it was but a step to the conscious search for incompletely sex-linked genes in man. Ordinary sex-linkage has of course been known for some time, and many such genes have been described during the course of these lectures. Y-chromosome genes have also been known for some years. Four such genes have been described, as follows.

Ichthyosis hystrix gravior (Maschin 1732). This mutation has occurred only once, and has since then been handed down from affected males to all their sons for six generations. The affected individuals at the age of a few weeks develop a dark thick rugged bark-like skin on the whole body except the face, palms, and soles.

Webbed toes (Schofield 1921). Not all types of webbing are inherited in this way, but in Schofield's pedigree the condition, involving the second and third toes, was passed on from affected males to all their sons for four

generations, fourteen affected males being included in the pedigree.

Keratoma dissipatum (Brauer 1913) is a condition in which small hard lesions are found on the hands and feet, chiefly on the palms and soles. Onset occurs after puberty, and the papules are not tender nor painful. Two families with this condition have been recorded, in each of which the anomaly behaved as a Y-borne gene.

Hypertrichosis of the ears (Tommasi 1907) is the fourth trait known to be dependent upon a gene carried on the Y-chromosome. For five generations this trait has been handed down from an affected male to all his sons. In this condition there is a dense growth of long hair on the ears, giving a very curious appearance to the 11 affected members of the pedigree. The onset of the growth of hair appeared at the age of 18 or 19.

The search for incompletely sex-linked genes in man has resulted to date in finding six such genes (Haldane 1936, Roberts 1940). Such genes will behave as ordinary autosomal factors of the type that we have become familiar with except for one thing: some families will yield too many affected males and normal females, while others will produce too many affected females and normal males. In the case of a dominant gene, the affected offspring of affected fathers will tend to be of the same sex as the paternal parent from whom the father received the gene. In the case of a recessive gene the situation is not so obvious, and the requisite statistical analysis is rather intricate.

Since mutant genes are usually rare, crossing-over cannot be studied between any two of them, but for those which are incompletely sex-linked, crossing-over can be

studied between the gene and sex, or more exactly between the gene and the unpaired nonhomologous portions of the X- and Y-chromosomes.

Consider a dominant gene, incompletely sex-linked. In order to study crossing-over, the father must be the affected parent, since in the mother crossing-over would merely move the gene from one X-chromosome to the other. In the father crossing-over changes the gene from the X- to the Y-chromosome, or vice versa (figure 23).

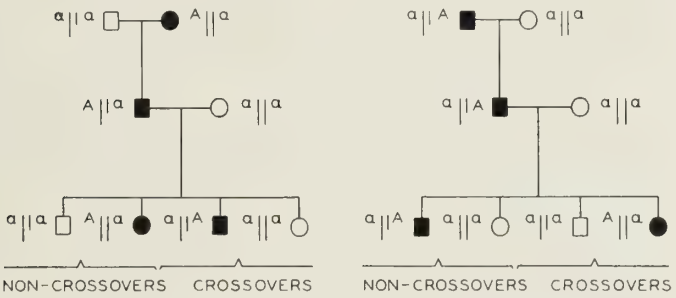

Fig. 23.—Diagrammatic representation of the method of determining incomplete sex-linkage in the case of a dominant mutant gene.

Studies on a series of pedigrees of dominant retinitis pigmentosa gave the following results (Haldane 1936): of 141 offspring of the same sex as the affected paternal grandparent, 81 were affected and 60 were not. Conversely, of 147 offspring of opposite sex to the affected paternal grandparent, 64 were affected and 83 were not. By reference to figure 23 it will be seen that the groups of 60 and 64 were crossovers, while the groups of 81 and 83 were non-crossovers. The percentage of crossing-over was thus 43. Closer examination revealed the fact that only about 40 per cent of the families showed significant

deviations from the 1:1 ratio, and in these the crossover value was 28 per cent.

Now consider a recessive gene, incompletely sex-linked. Again we must search for crossing-over between the X- and Y-chromosomes of heterozygous males. In recessive inheritance, however, the parents and grandparents of affected individuals will usually be normal, so that we cannot tell whether a heterozygous male received the gene from his father or from his mother. Nevertheless, some families will yield too many affected males and normal females, while others will yield the reverse. The procedure in analyzing recessive incomplete sex linkage is much more difficult than that in dominant incomplete sex linkage. In spite of this, five recessive genes have provided good evidence for being inherited on the homologous portions of the sex chromosomes, that is, of being incompletely sex-linked.

The six genes known to be inherited in this way, and which provide the first material for a human chromosome map, are as follows.

Total color-blindness. A rare type of color-blindness in which everything appears in shades of gray or in black and white. In many cases there are further defects such as nystagmus, photophobia, and amblyopia.

Xeroderma pigmentosum (Kaposi 1882) is an abnormal sensitivity of the skin to light, involving marked freckling and reddening of the skin. The freckles remain even in cold weather and become larger, more numerous, and more heavily pigmented. The disease progresses to include malignant changes and is usually fatal.

Oguchi's disease is a form of night-blindness in which

ophthalmoscopic examination reveals a golden appearance of the fundus when it is adapted to light.

Recessive epidermolysis bullosa is described in chapter 5. It is a severe, malignant, frequently fatal type of epidermolysis.

Retinitis pigmentosa is described in chapter 4. There are several types, of which those incompletely sex-linked are, first, a recessive form unassociated with deafness, and, second, a dominant form.

These six genes are known to be carried on the homologous portions of the X- and Y-chromosomes, and their

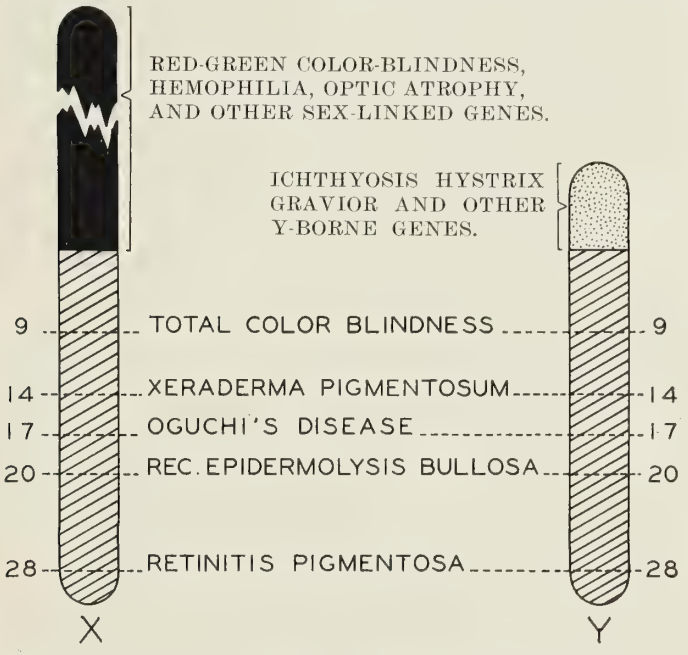

Fig. 24.—A map of the sex chromosomes, based on the work of Haldane.

crossover proportions with the nonhomologous portions have been calculated. From these Haldane has constructed the first linkage map of a human chromosome (figure 24).

When maps such as this are available for the autosomes of man, we shall have gone a long way towards putting genetic prognosis on a sound scientific basis. The field of research in human heredity and medical genetics is wide open.

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